



Supporting Information

for

Enantioselective total synthesis of putative dihydrorosefuran, a monoterpene with an unique 2,5-dihydrofuran structure

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Experimental procedures, characterization of other substances, and copies of IR, NMR spectra and HPLC chromatograms

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Experimental section

General remarks

NMR spectra were recorded on Bruker Nanobay Avance III HD 300 MHz, Avance III HD 500 MHz and Avance III HD 600 MHz spectrometers. Proton-decoupled ^{13}C NMR spectra and DEPT-135 were measured in all cases. When required, HSQC and HMBC experiments were used for signal assignment. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in hertz (Hz). Chemical shifts are reported using CDCl_3 as internal reference. IR Spectra were recorded with a Bruker Alpha spectrometer. Mass spectra were recorded in a Waters Xevo by LC-QToF-MS by electrospray ionization. The samples were analyzed by high performance liquid chromatography (HPLC) using an Agilent 1100 quaternary pump. The chromatographic columns used were Daicel Chiracel OD-H and Daicel Chiralpack IA. An isocratic elution of a mixture of hexane/isopronaol is all that is needed to analyze the compounds, and filtration is the only sample preparation required before injection. Separations are performed at a temperature of 25 °C and at flow rates of 0.4–0.5 mL/min. A UV detector with a diode array was also used and the compounds of interest were quantified at wavelengths 210 nm. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2 mm DC-Fertigfolien Alugram® XtraSil G/UV254 silica gel plates. The TLC plates were visualized with UV light and 7% phosphomolybdic acid or KMnO_4 in water/heat. Flash chromatography was performed on silicagel 60 (0.04–0.06 mm). Commercially available chemicals were obtained from Aldrich Chemical Co., Acros, Alfa Aesar, and TCI and were used as received. In all experiments involving Ti(III), reactions were performed under argon atmosphere, using oven-dried glassware in all cases. THF was distilled from Na/benzophenone under argon, and was deoxygenated prior to use.

Synthesis of ethyl 4-oxobutanoate (**4**)

Ozone was bubbled through a solution of ethyl pent-4-enoate (1.22 g, 9.52 mmol) in DCM (20 mL) at $-78\text{ }^{\circ}\text{C}$ until the solution turned blue. Then, PPh_3 (3 g, 11.42 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed in vacuum and the residue purified by silica gel flash column chromatography (pentane/diethyl ether 7:3) to afford ethyl 4-oxobutanoate (**4**, 935 mg, 76%) as colorless oil. ^1H NMR and IR spectral data are in agreement with literature values [1]. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , DEPT) δ (ppm) 200.1 (CH), 172.3 (C), 60.8 (CH_2), 38.6 (CH_2), 26.6 (CH_2), 14.2 (CH_3).

Synthesis of 2,6-dimethylocta-6,7-diene-2,5-diol (**7**)

To a solution of methyllmagnesium bromide (3 M in Et_2O , 0.14 mL, 0.43 mmol) in anhydrous Et_2O (1 mL), a solution of 5-(buta-2,3-dien-2-yl)-dihydrofuran-2(3*H*)-one (**5**, 24 mg, 0.17 mmol) in anhydrous diethyl ether (0.6 mL) was slowly added. The mixture was stirred under N_2 at room temperature for 40 min. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 . The solvent was removed in vacuum to give **7** (24 mg, 83%) as colorless oil. IR (ATR) ν (cm^{-1}) 3376, 2970, 2928, 2872, 1959, 1646, 1377, 1262, 1213, 1152, 1058, 1024, 907, 846, 803. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 4.80 (dq, $J = 5.4, 3.0$ Hz, 2H), 4.07 (m, 1H), 2.08 (br s, 2H), 1.73 (t, $J = 3.0$ Hz, 3H), 1.64 (m, 4H), 1.25 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , DEPT) δ (ppm) 204.9 (C), 102.0 (C), 76.8 (CH_2), 72.7 (CH), 70.7 (C), 39.4 (CH_2), 29.8 (CH_2), 29.5 (CH_3), 29.3 (CH_3), 14.5 (CH_3). HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{19}\text{O}_2$ 171.1385; found 171.1397.

Silver(I)-promoted cyclization of 2,6-dimethylocta-6,7-diene-2,5-diol (**7**)

A solution of the allenol **7** (16 mg, 0.09 mmol) in acetone (1.5 mL) was added to a suspension of AgNO_3 (30 mg, 0.19 mmol) in acetone (1.5 mL) in the absence of light, and the mixture was stirred at $40\text{ }^{\circ}\text{C}$ overnight. Brine was added and the mixture was extracted with Et_2O . The organic phase was dried over anhydrous MgSO_4 , and concentrated under reduced pressure to

afford 2-methyl-4-(3-methyl-2,5-dihydrofuran-2-yl)butan-2-ol (**6**, 12 mg, 75%) that was isolated as colorless oil.

Enzymatic kinetic resolution of α -allenic alcohols

Based on the previously literature procedure [2], the reaction of ethyl 4-hydroxy-5-methylhepta-5,6-dienoate (**3**, 0.13 g, 0.71 mmol), lipase AK (35.5 mg, 20,000 U/g) and vinyl acetate (0.53 mL, 5.68 mmol) in methyl *tert*-butyl ether (7 mL), after purification by flash chromatography (*n*-hexane/Et₂O 7:3), provided the desired compounds including ethyl (*S*)-4-hydroxy-5-methylhepta-5,6-dienoate ((-)-(*S*)-**3**, 60 mg, 46%, 90% ee), $[\alpha]_D^{25}$ -9.2 (c 0.037, CHCl₃), and ethyl (*R*)-4-acetoxy-5-methylhepta-5,6-dienoate ((+)-(*R*)-**9**, 63 mg, 39%, 95% ee), $[\alpha]_D^{25}$ +115 (c 0.042, CHCl₃), as light yellow oils. Enantiomeric excess (ee) was determined by chiral HPLC (see HPLC Data). Compound (+)-(*R*)-**9**: IR (ATR) ν (cm⁻¹) 2982, 2937, 1961, 1731, 1431, 1371, 1227, 1178, 1020, 854. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 5.23 (t, *J* = 6.5 Hz, 1H), 4.78 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 8.1 Hz, 2H), 2.08 (s, 3H), 2.03 (m, 2H), 1.70 (t, *J* = 3.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃, DEPT) δ (ppm) 206.3 (C), 172.9 (C), 170.3 (C), 97.8 (C), 76.5 (CH₂), 73.4 (CH), 60.5 (CH₂), 30.3 (CH₂), 27.7 (CH₂), 21.0 (CH₃), 14.7 (CH₃), 14.2 (CH₃). HRMS (ESI/Q-TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₉O₄ 227.1283; found 227.1260.

Synthesis of (*R*)-2,6-dimethylocta-6,7-diene-2,5-diol ((+)-(*R*)-**7**)

A solution of ethyl (*R*)-4-acetoxy-5-methylhepta-5,6-dienoate ((+)-(*R*)-**9**, 60 mg, 0.27 mmol) in anhydrous Et₂O (1 mL) was slowly added to a solution of methylmagnesium bromide (3 M in Et₂O, 0.45 mL, 1.35 mmol) in anhydrous Et₂O (1.5 mL). The mixture was stirred under N₂ at room temperature for 5 h. The reaction was quenched with saturated NH₄Cl and extracted with ethyl acetate. The combined organic layer was washed with saturated NaHCO₃ and brine, dried with anhydrous MgSO₄. The solvent was evaporated in vacuum to give (+)-(*R*)-**7** (31.2 mg, 67%) $[\alpha]_D^{25}$ +17.5 (c 0.026, CHCl₃) as colorless oil.

Synthesis of the Mosher's derivatives of compound (-)-(S)-3

a) DCC (60 mg, 0.29 mmol), DMAP (7 mg, 0.06 mmol) and (S)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (65 mg, 0.27 mmol) were added to a solution of (-)-(S)-3 (21 mg, 0.11 mmol) in CH₂Cl₂ (7 mL) at 0 °C. The mixture was stirred at room temperature overnight. CH₂Cl₂ (15 mL) was added and the organic layer was washed with NaOH (2 N), HCl (5%) and brine. After drying over anhydrous MgSO₄, the solvent was removed in vacuum. The residue was purified by flash chromatography (*n*-hexane/EtOAc 8:2), to provide ethyl (S)-5-methyl-4-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hepta-5,6-dienoate ((4S,2'S)-8) as a white solid (29 mg, 66%) and 5-(buta-2,3-dien-2-yl)dihydrofuran-2(3*H*)-one (5, 5 mg, 28%). Compound (4S,2'S)-8: $[\alpha]^{25}_D$ -138 (c 0.013, CHCl₃), ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.54 (m, 2H), 7.40 (m, 3H), 5.44 (t, *J* = 6.7 Hz, 1H), 4.82 (dq, *J* = 10.8, 3.0, 1.2 Hz, 1H), 4.76 (dq, *J* = 10.8, 3.0, 1.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.55 (s, 3H), 2.24 (m, 2H), 2.03 (m, 2H), 1.70 (t, *J* = 3.2 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃, DEPT) δ (ppm) 207.0 (C), 172.5 (C), 165.9 (C), 132.3 (C), 129.6 (CH), 128.4 (CH), 127.4 (CH), 125.3 (C, q, *J*_{C-F} = 287 Hz), 96.9 (C), 84.6 (C, q, *J*_{C-F} = 27 Hz), 77.0 (CH₂), 76.9 (CH), 60.6 (CH₂), 55.5 (CH₃), 29.8 (CH₂), 27.6 (CH₂), 14.6 (CH₃), 14.2 (CH₃). ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm) -71.31 (s).

b) The same protocol was repeated using (R)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetic acid. Ethyl (S)-5-methyl-4-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hepta-5,6-dienoate ((4S,2'R)-8, 32 mg, 73%) and 5-(buta-2,3-dien-2-yl)dihydrofuran-2(3*H*)-one (5, 4 mg, 22%) were obtained. Compound (4S,2'R)-8: $[\alpha]^{25}_D$ +10.1 (c 0.0063, CHCl₃), ¹H NMR (600 MHz, CDCl₃) δ (ppm) 7.53 (m, 2H), 7.40 (m, 3H), 5.42 (t, *J* = 6.8 Hz, 1H), 4.79 (m, 1H), 4.67 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 2.34 (m, 2H), 2.09 (q, *J* = 7.8 Hz, 2H), 1.58 (t, *J* = 3.6 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃, DEPT) δ (ppm) 207.0 (C), 172.5 (C), 165.9 (C), 132.2 (C), 129.6 (CH), 128.4 (CH), 127.4 (CH), 127.0 (C, q, *J*_{C-F} = 287 Hz), 96.7

(C), 84.6 (C, q, $J_{C-F} = 27$ Hz), 77.2 (CH₂), 76.8 (CH), 60.7 (CH₂), 55.5 (CH₃), 30.1 (CH₂), 27.6 (CH₂), 14.2 (CH₃). ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm) -71.50 (s).

Synthesis of the Mosher's derivative of racemic compound ($\pm$)-**3**

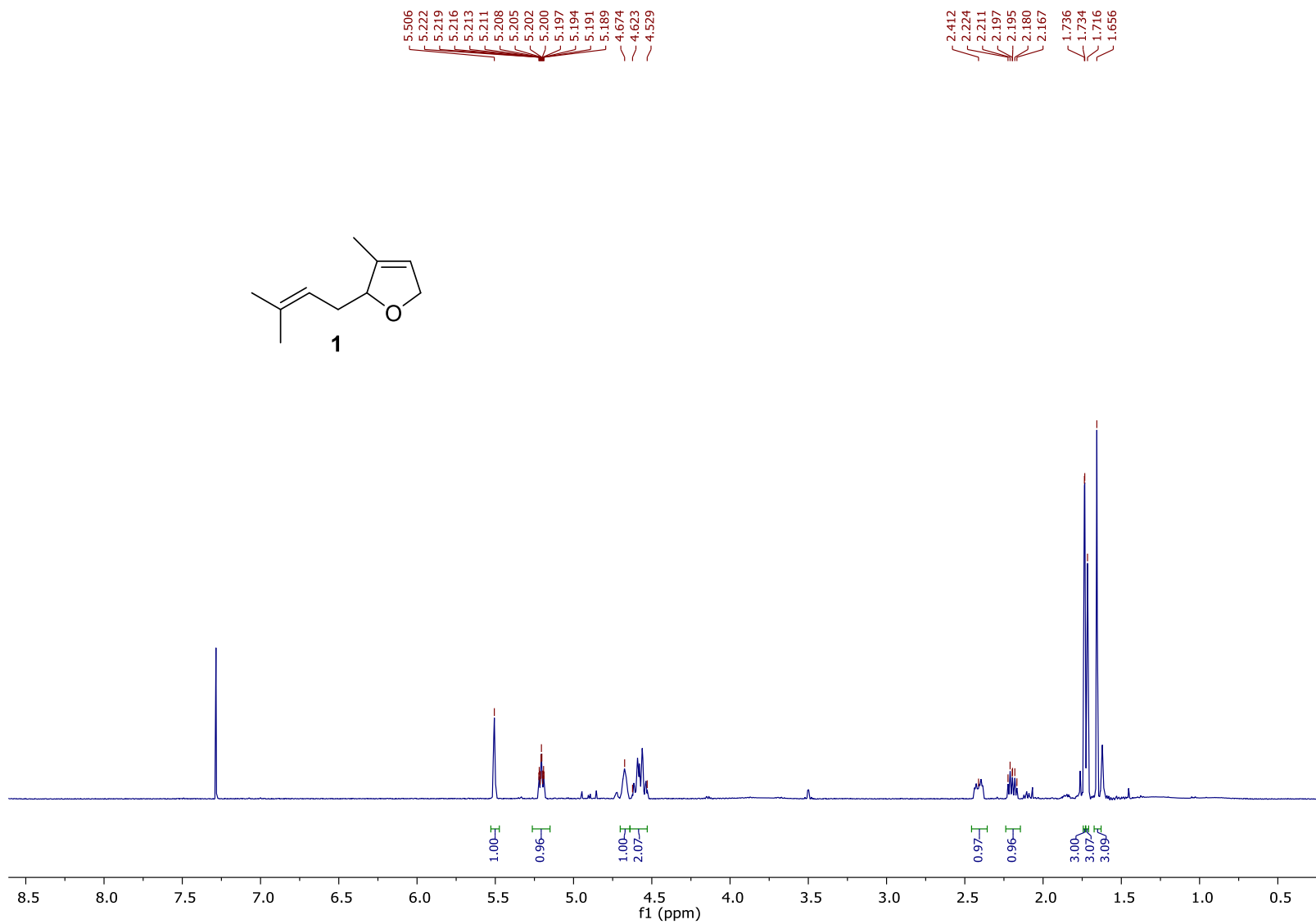
Compound **3** (15.8 mg, 0.09 mmol), DCC (46 mg, 0.22 mmol), DMAP (5.50 mg, 0.045 mmol) and (S)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (53.70 mg, 0.26 mmol), according to mentioned procedure, afforded compound **8** (11 mg, 31%) (as a mixture of inseparable isomers (4*S*,2'*S*)-**8**, and (4*R*,2'*S*)-**8**), and 5-(buta-2,3-dien-2-yl)dihydrofuran-2(3*H*)-one (**5**, 5.4 mg, 43%).

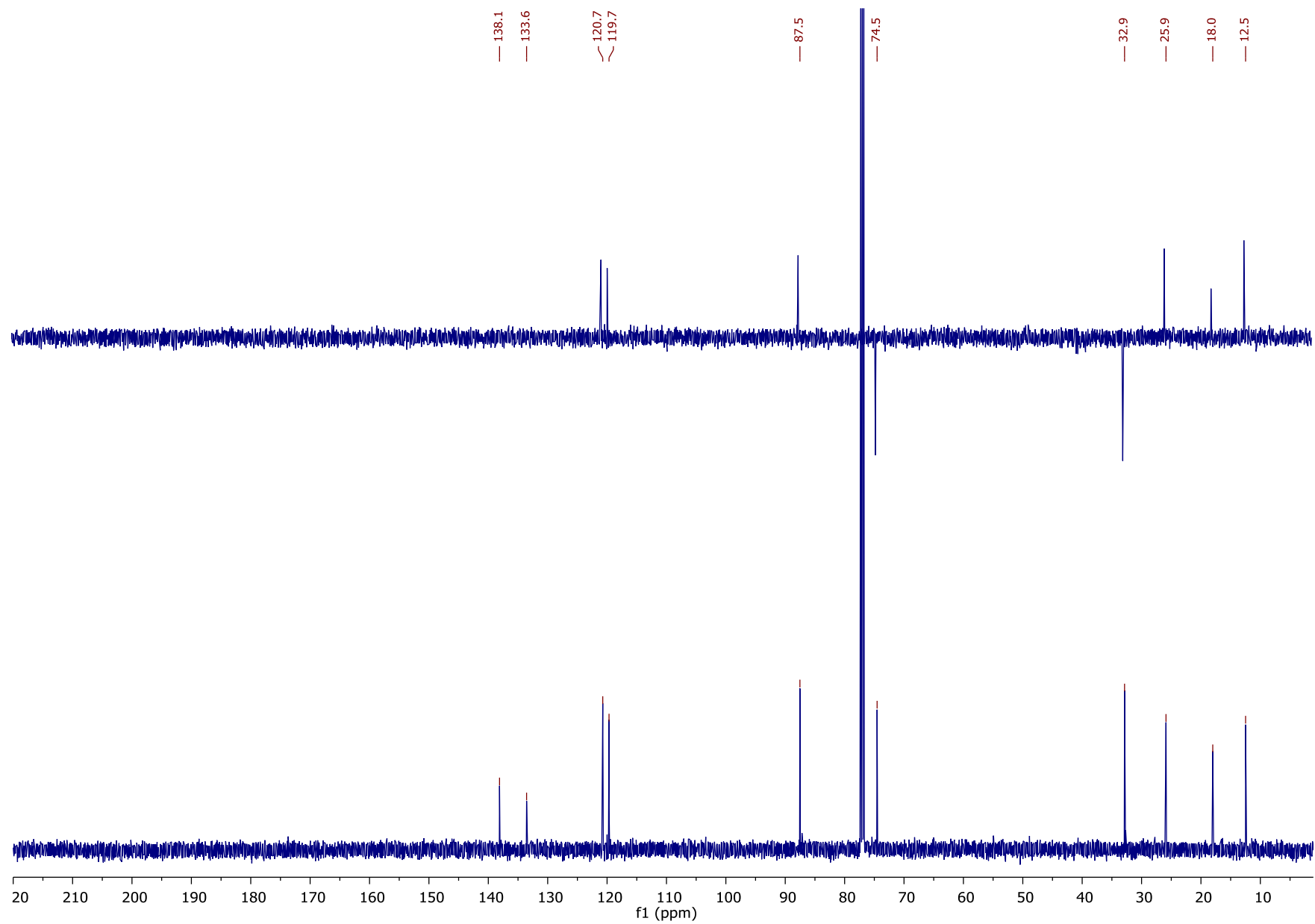
References

- [1] Smith, A. B.; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113* (6), 2071-2092. <https://doi.org/10.1021/ja00006a029>
- [2] Li, W.; Lin, Z.; Chen, L.; Tian, X.; Wang, Y.; Huang, S.-H.; Hong, R. *Tetrahedron Lett.* **2016**, *57* (5), 603-606. <https://doi.org/10.1016/j.tetlet.2015.12.098>

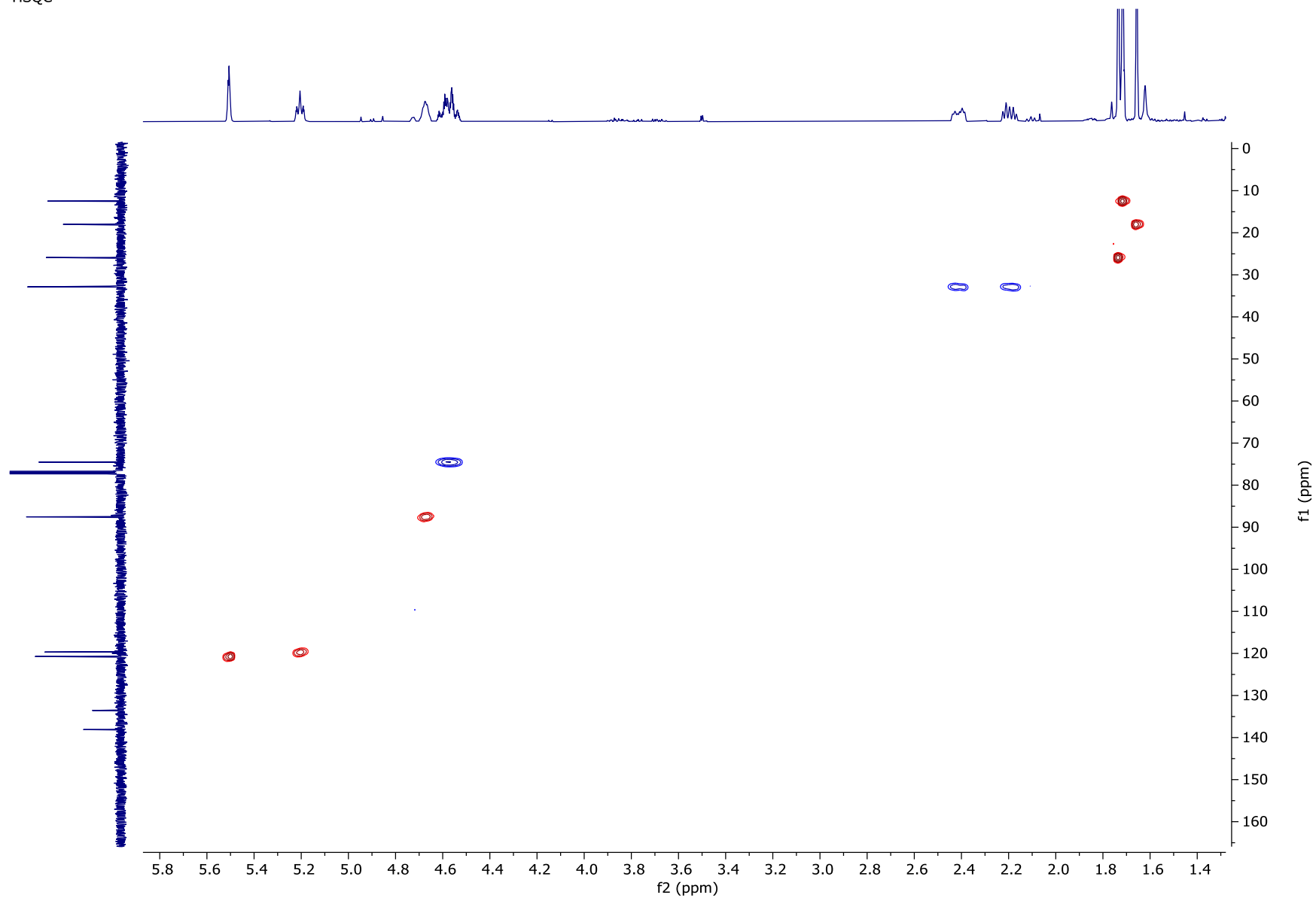
NMR and IR spectra

^1H NMR, DEPT 135, ^{13}C NMR, HSQC, HMBC and IR of 3-methyl-2-(3-methylbut-2-en-1-yl)-2,5-dihydrofuran (**1**)

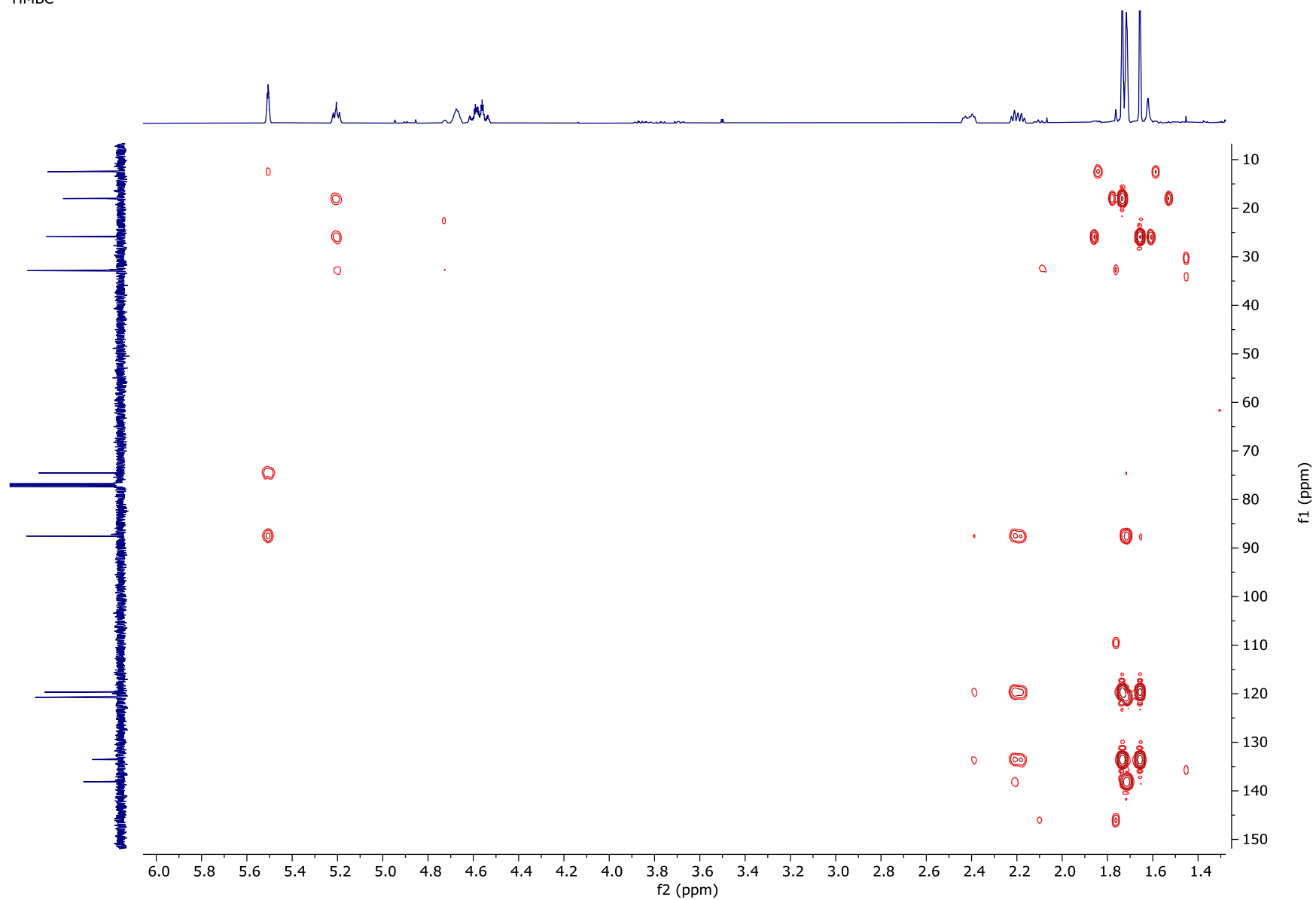


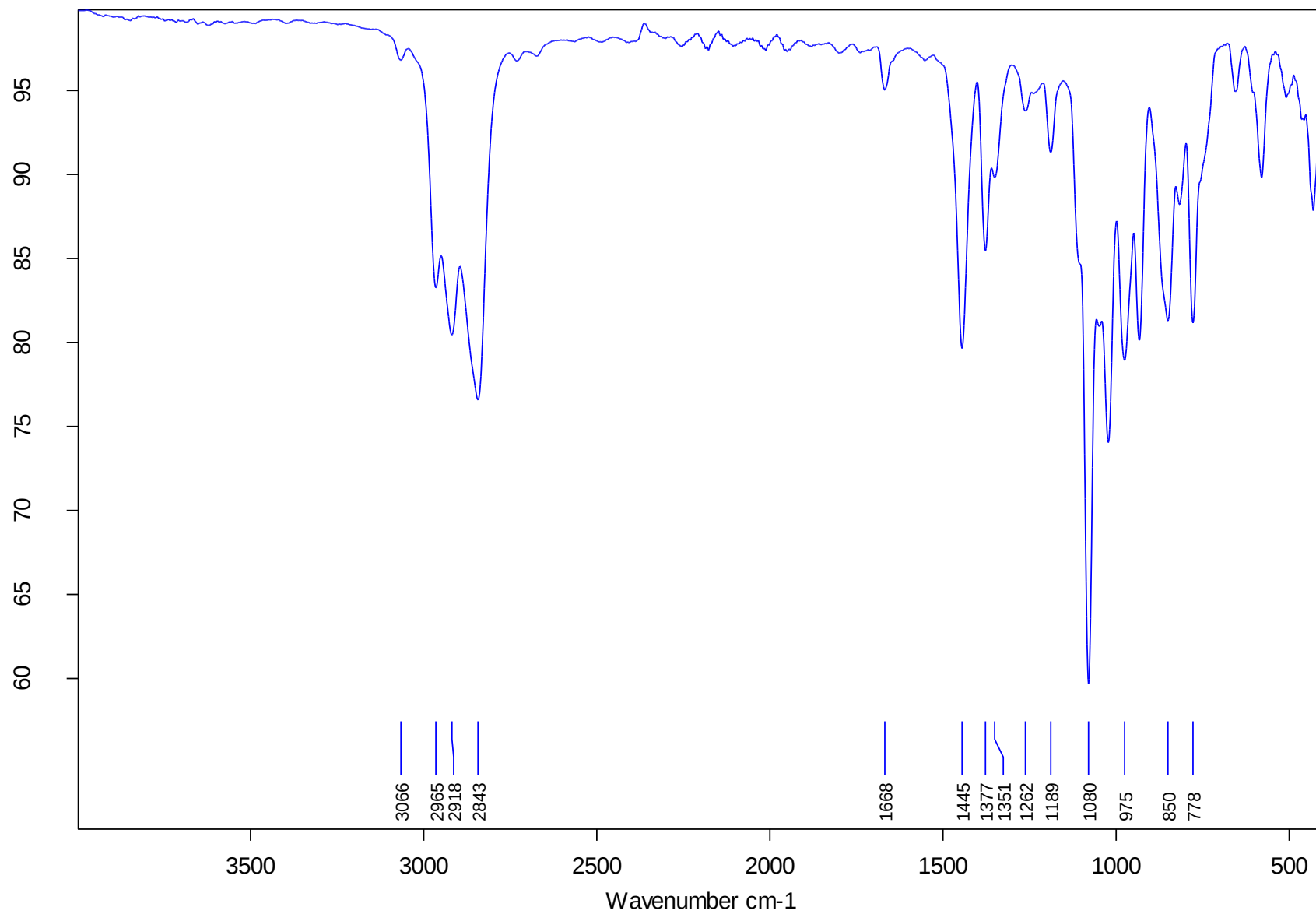


HSQC

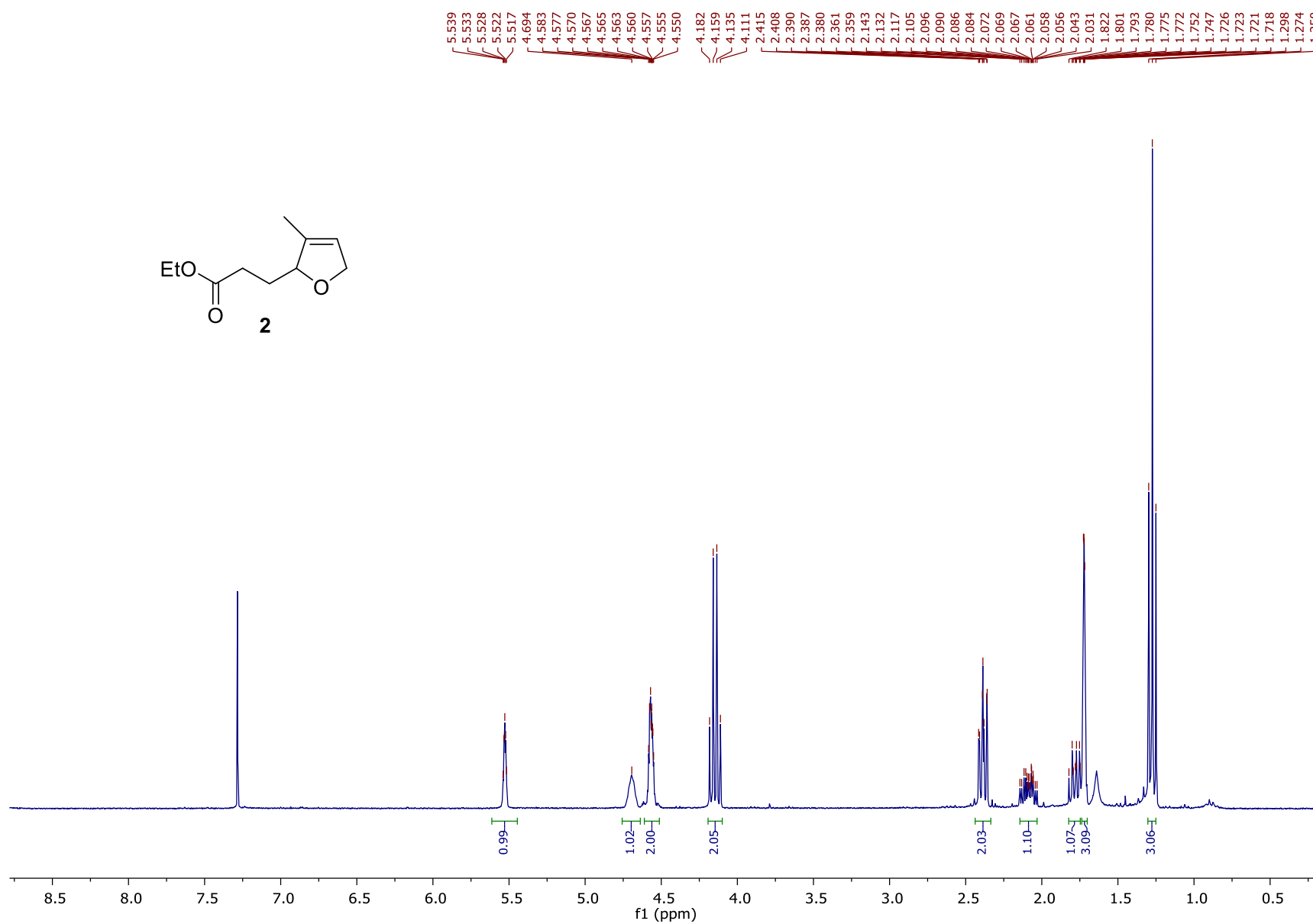


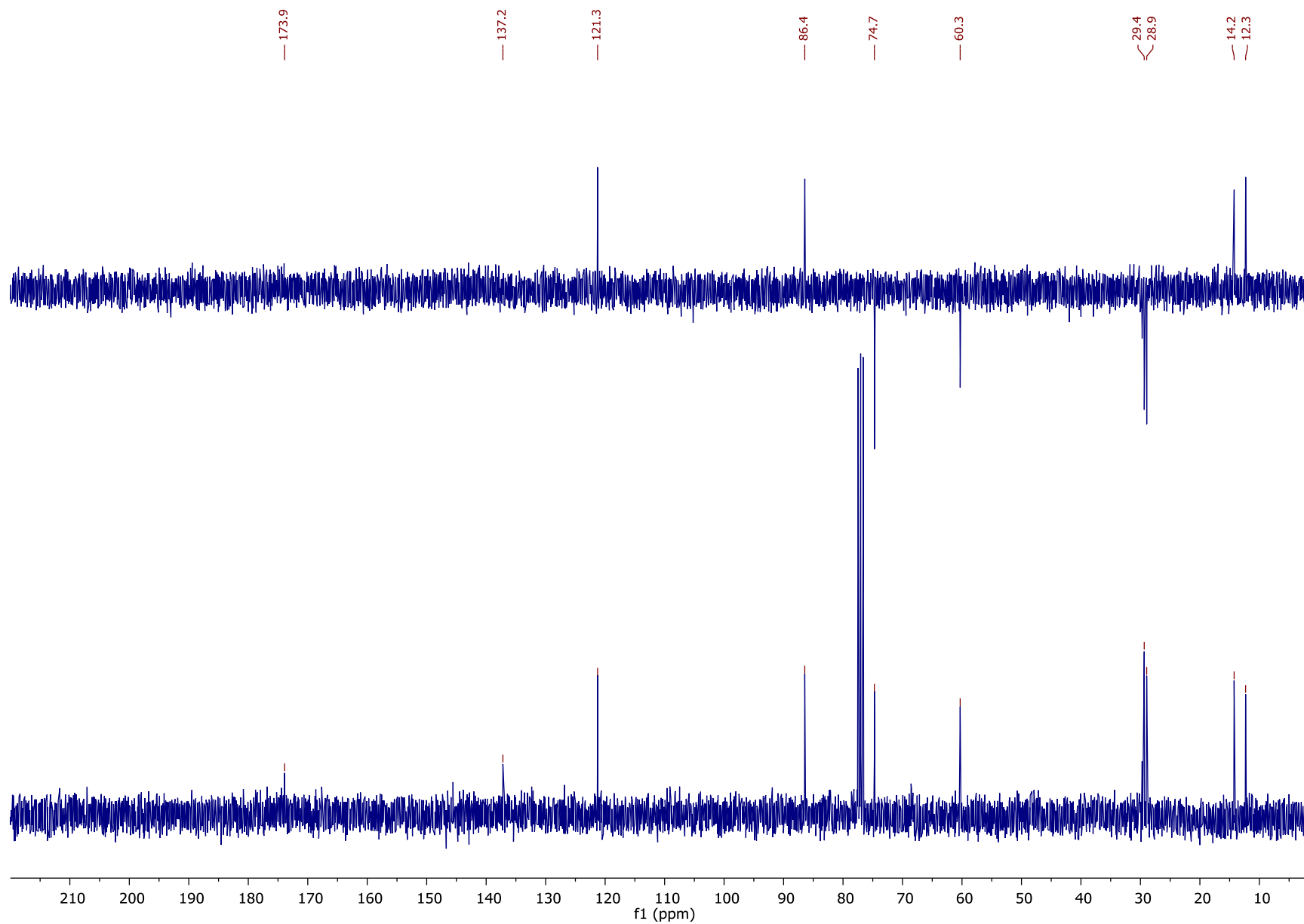
HMBC

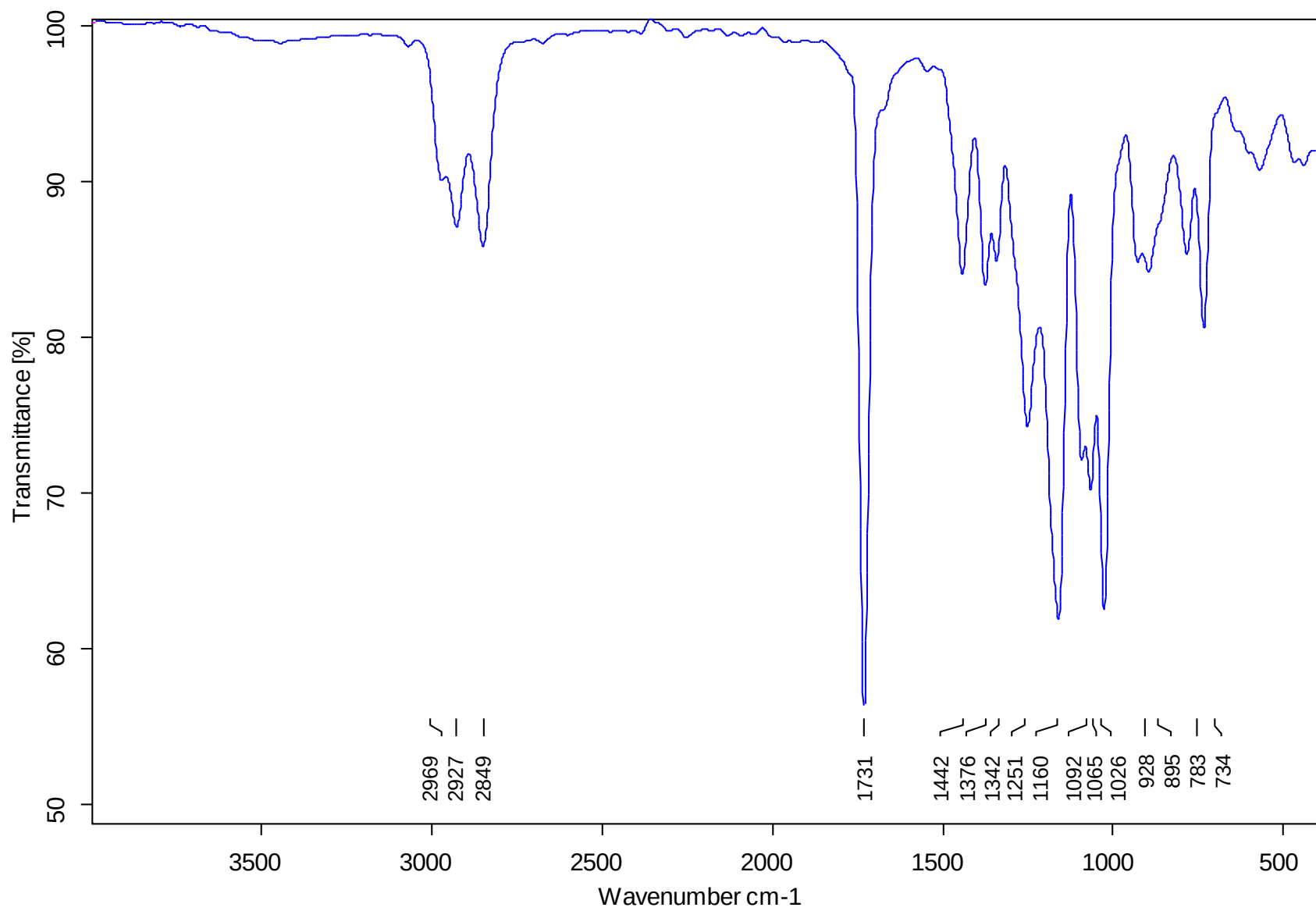




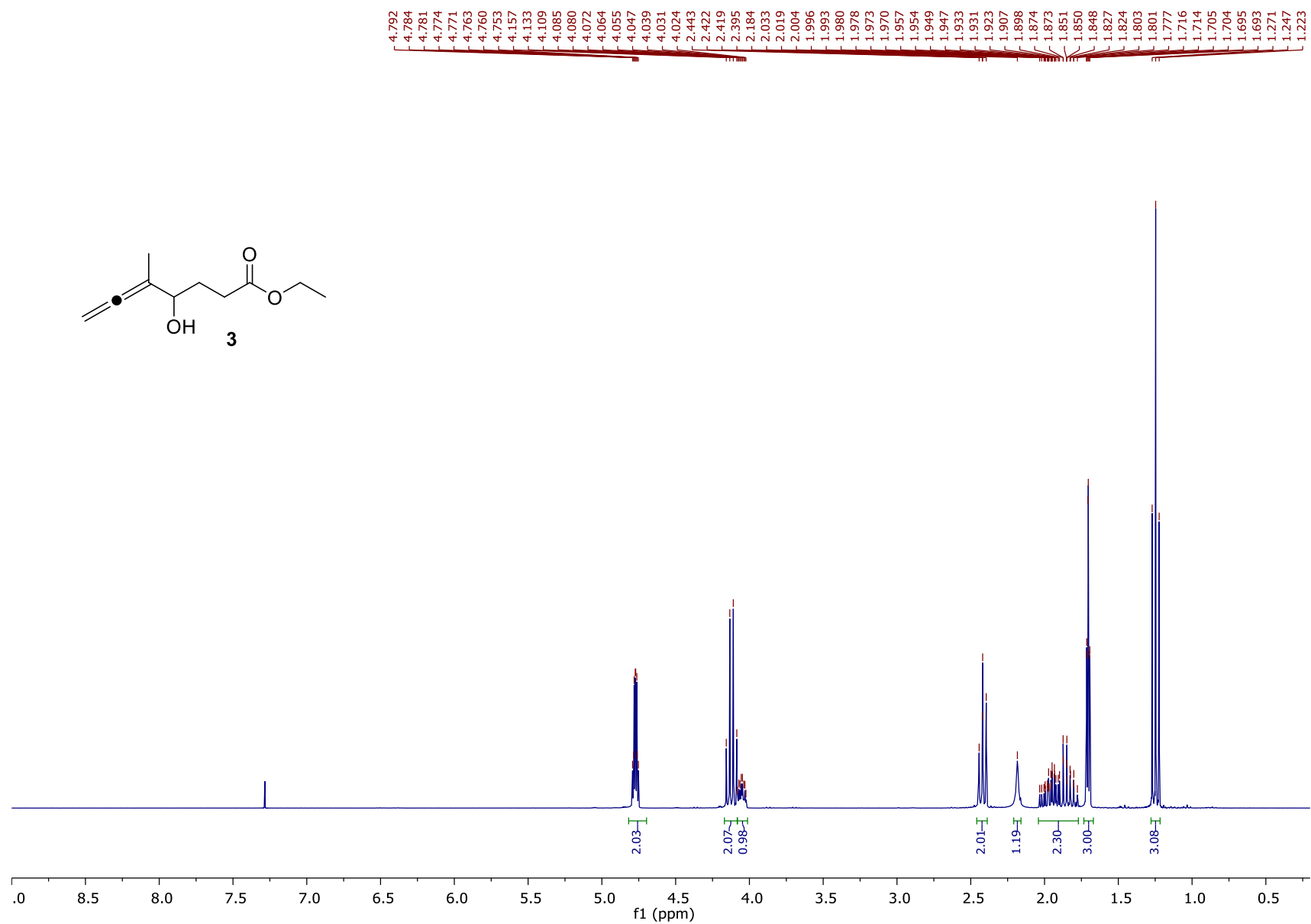
^1H NMR, DEPT 135, ^{13}C NMR and IR of ethyl 3-(3-methyl-2,5-dihydrofuran-2-yl)propanoate (**2**)

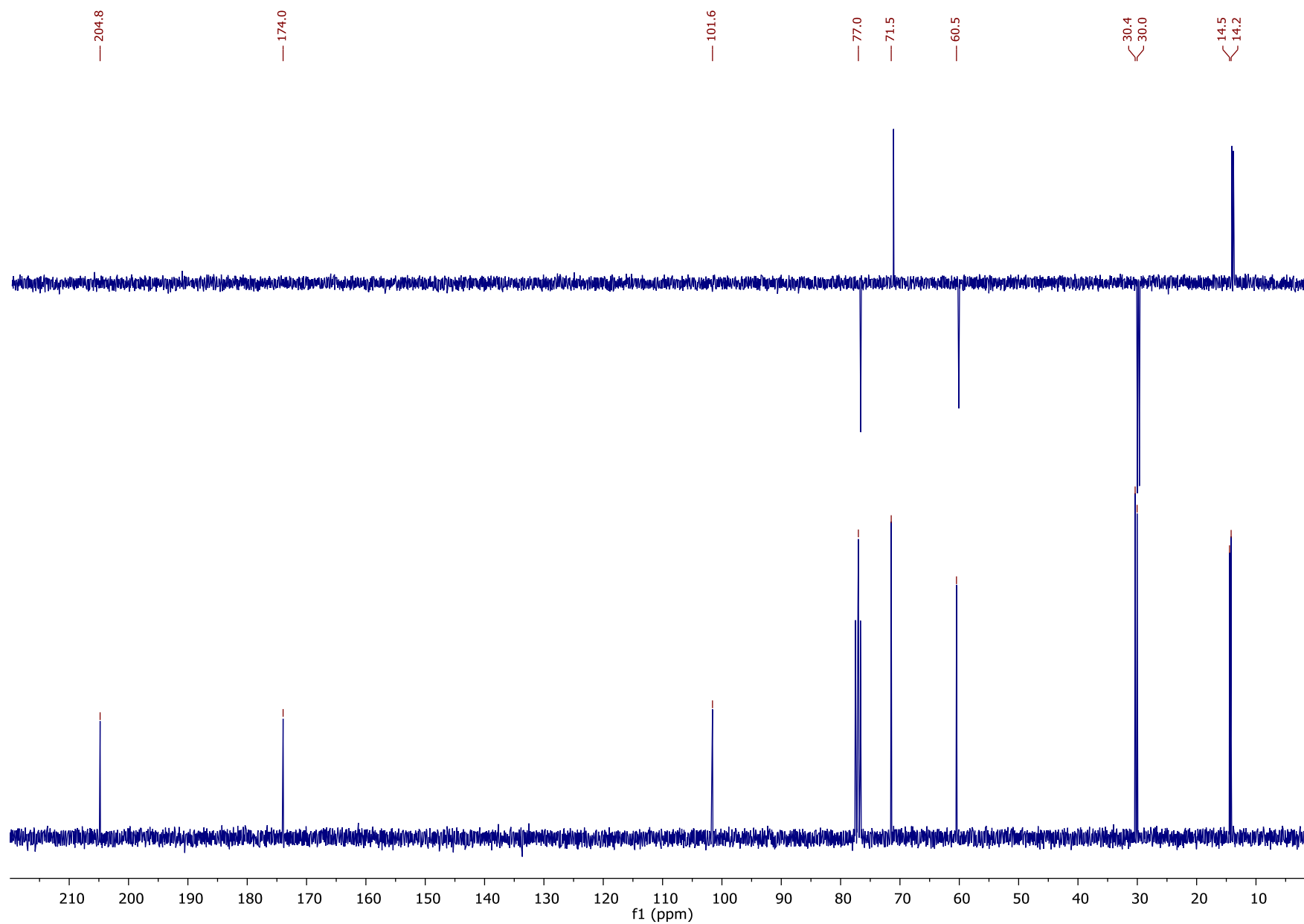


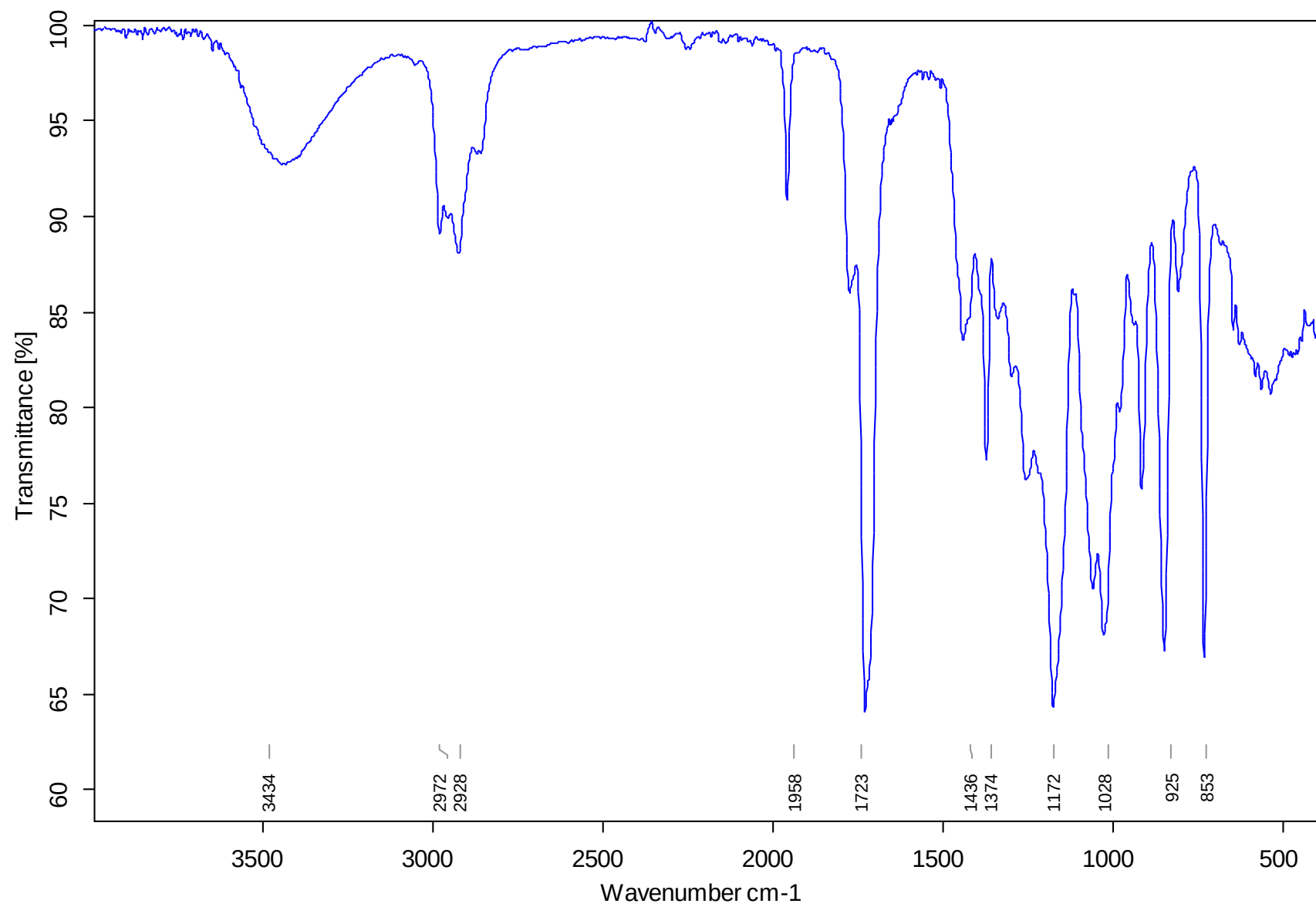




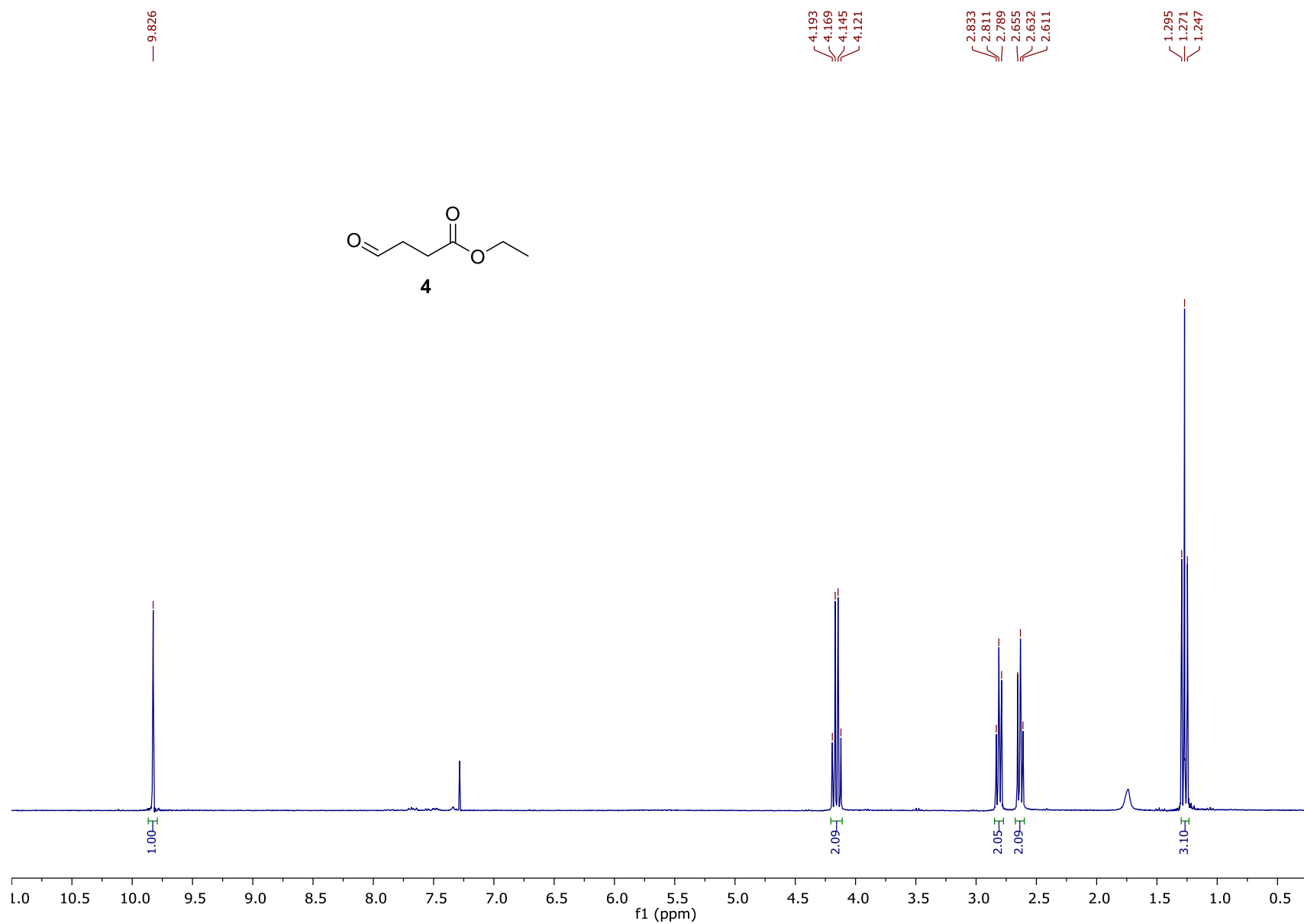
^1H NMR, DEPT 135, ^{13}C NMR and IR of ethyl 4-hydroxy-5-methylhepta-5,6-dienoate (**3**)

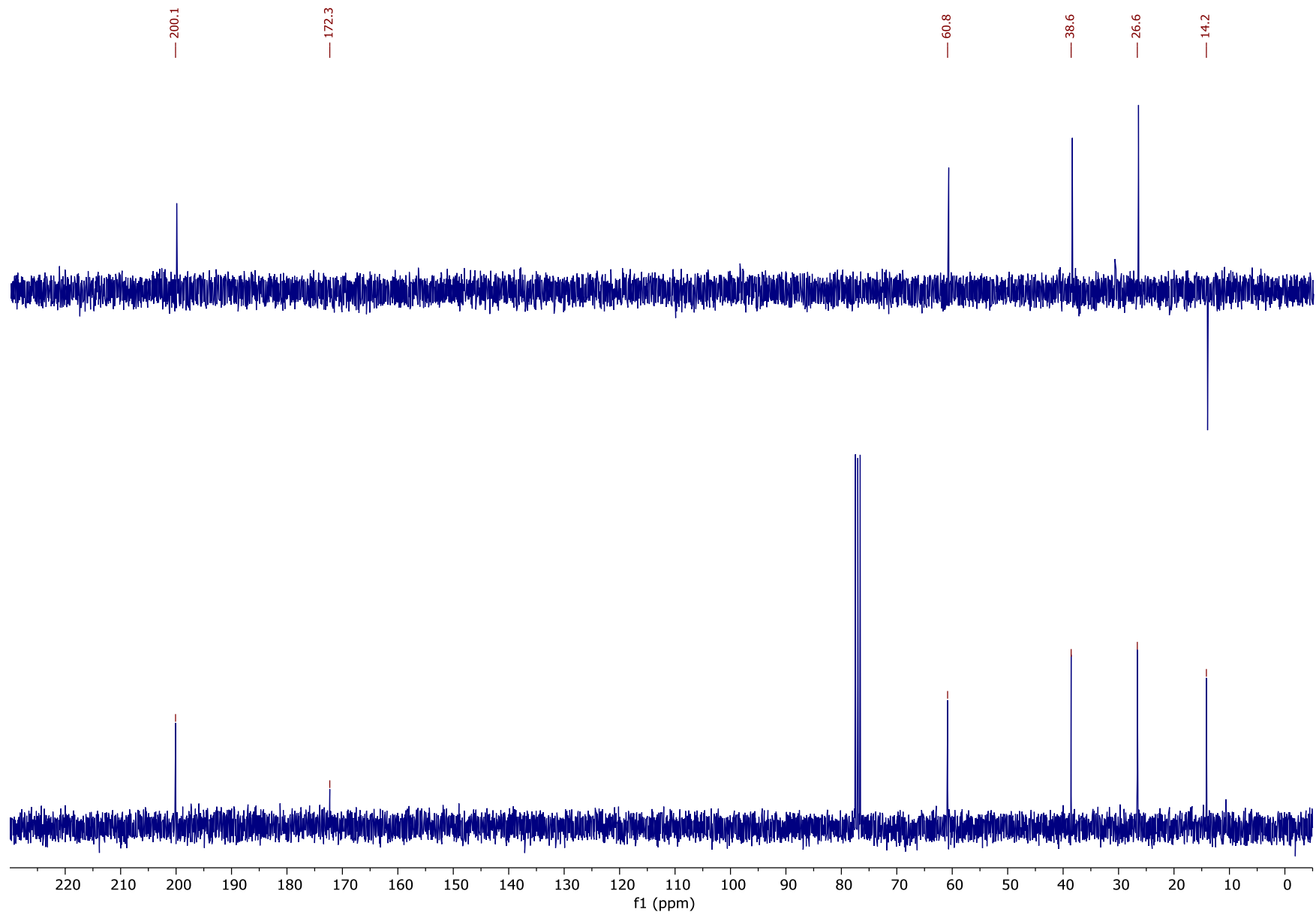


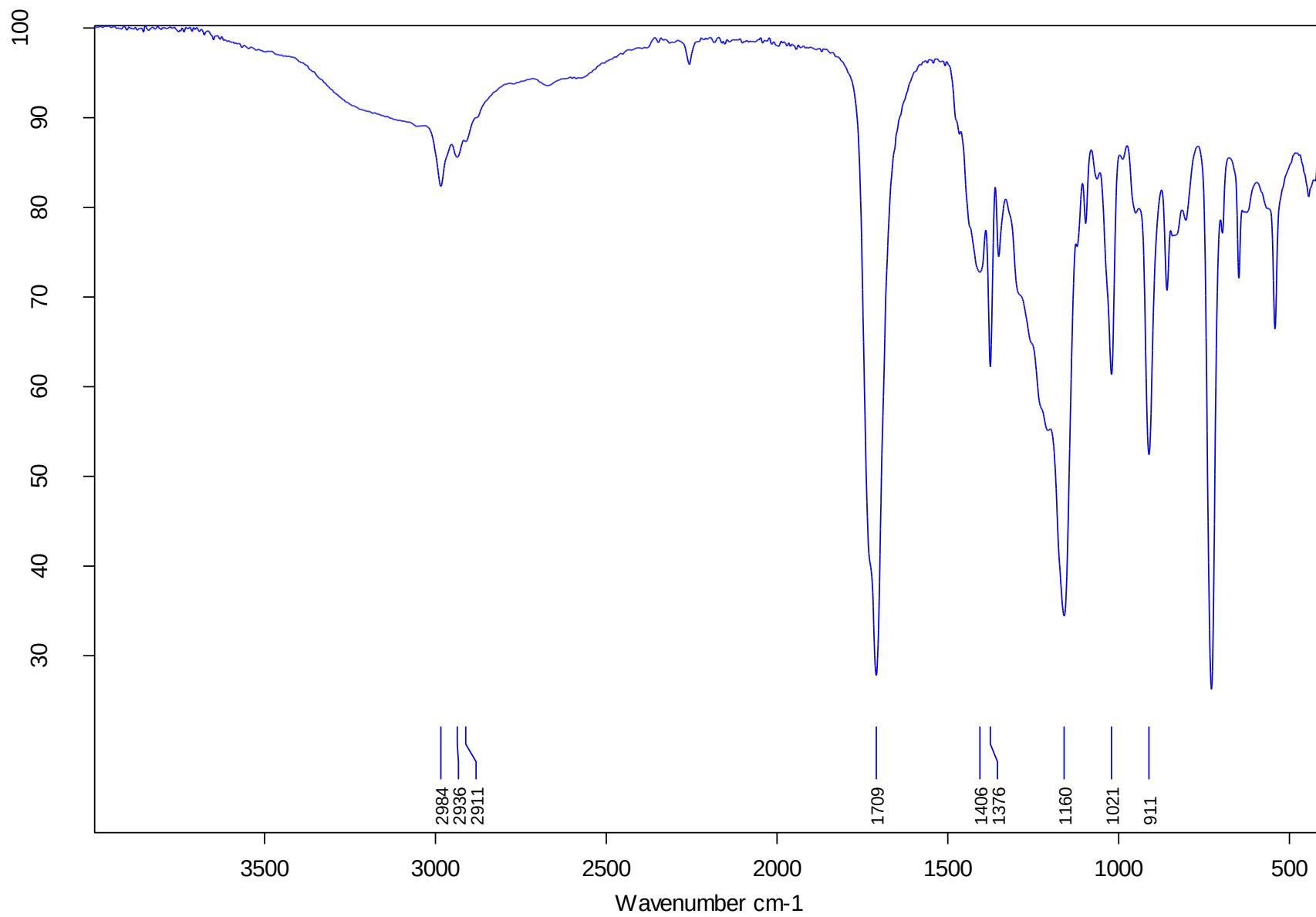




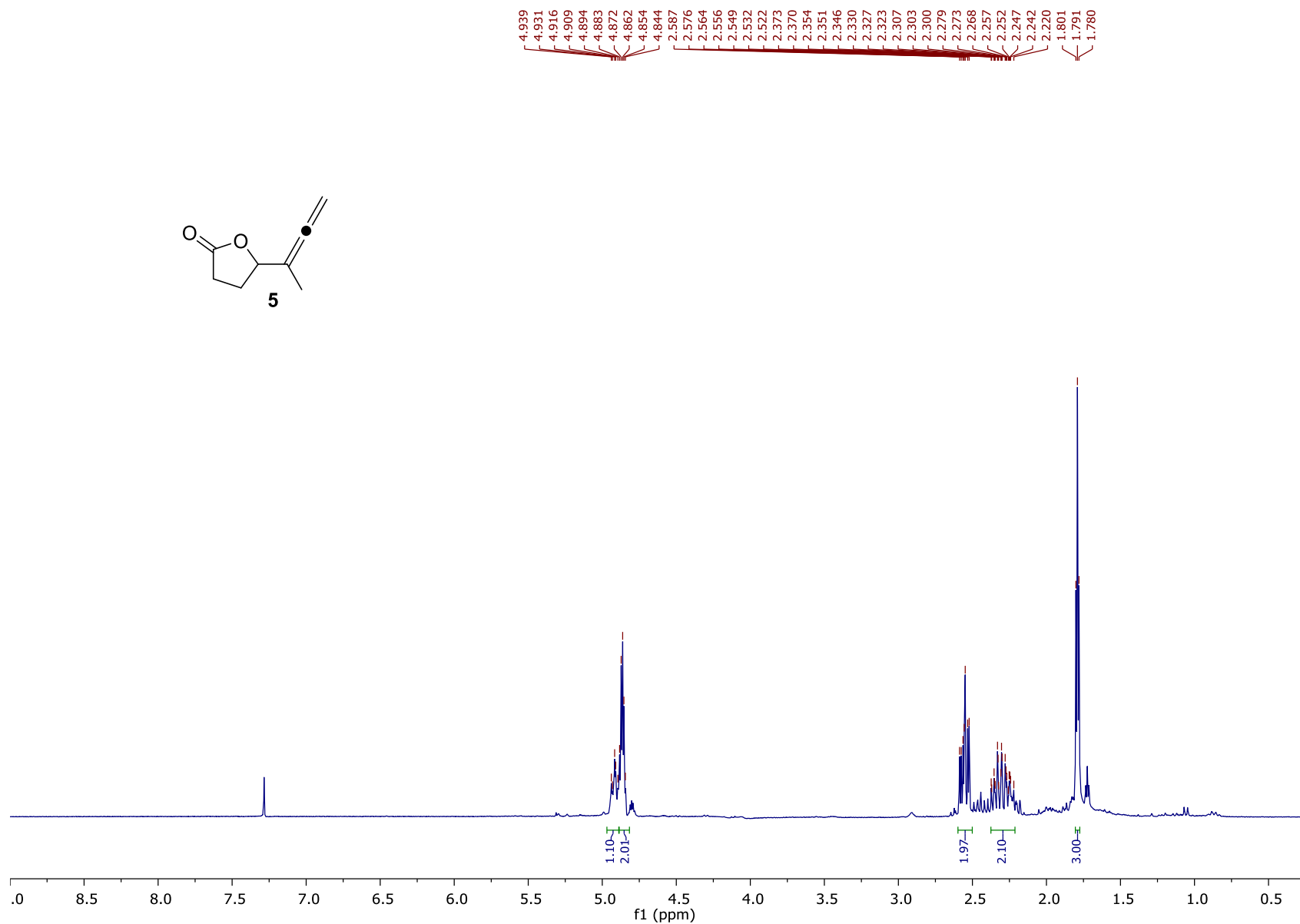
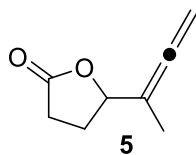
^1H NMR, DEPT 135, ^{13}C NMR and IR of ethyl 4-oxobutanoate (**4**)

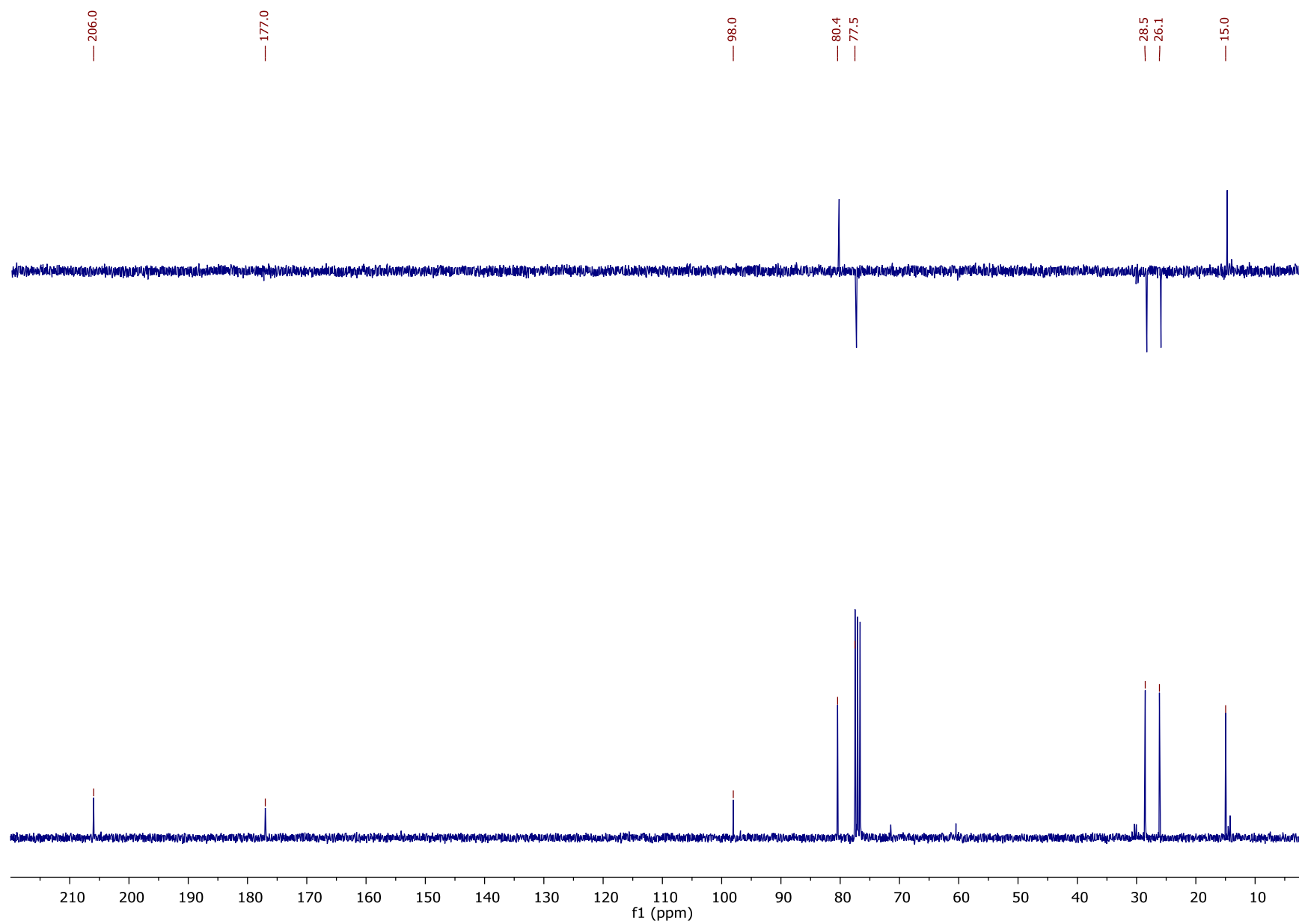


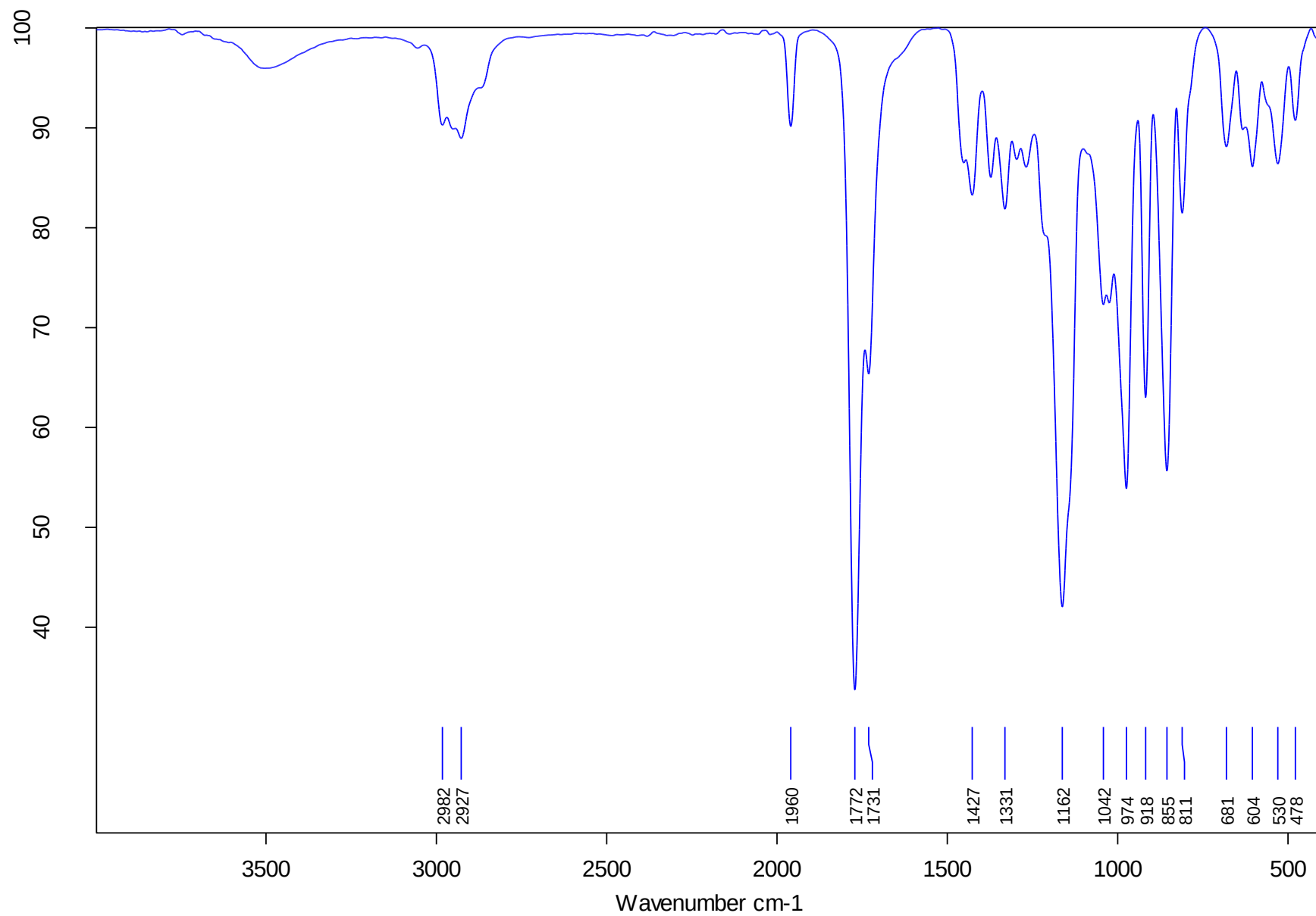




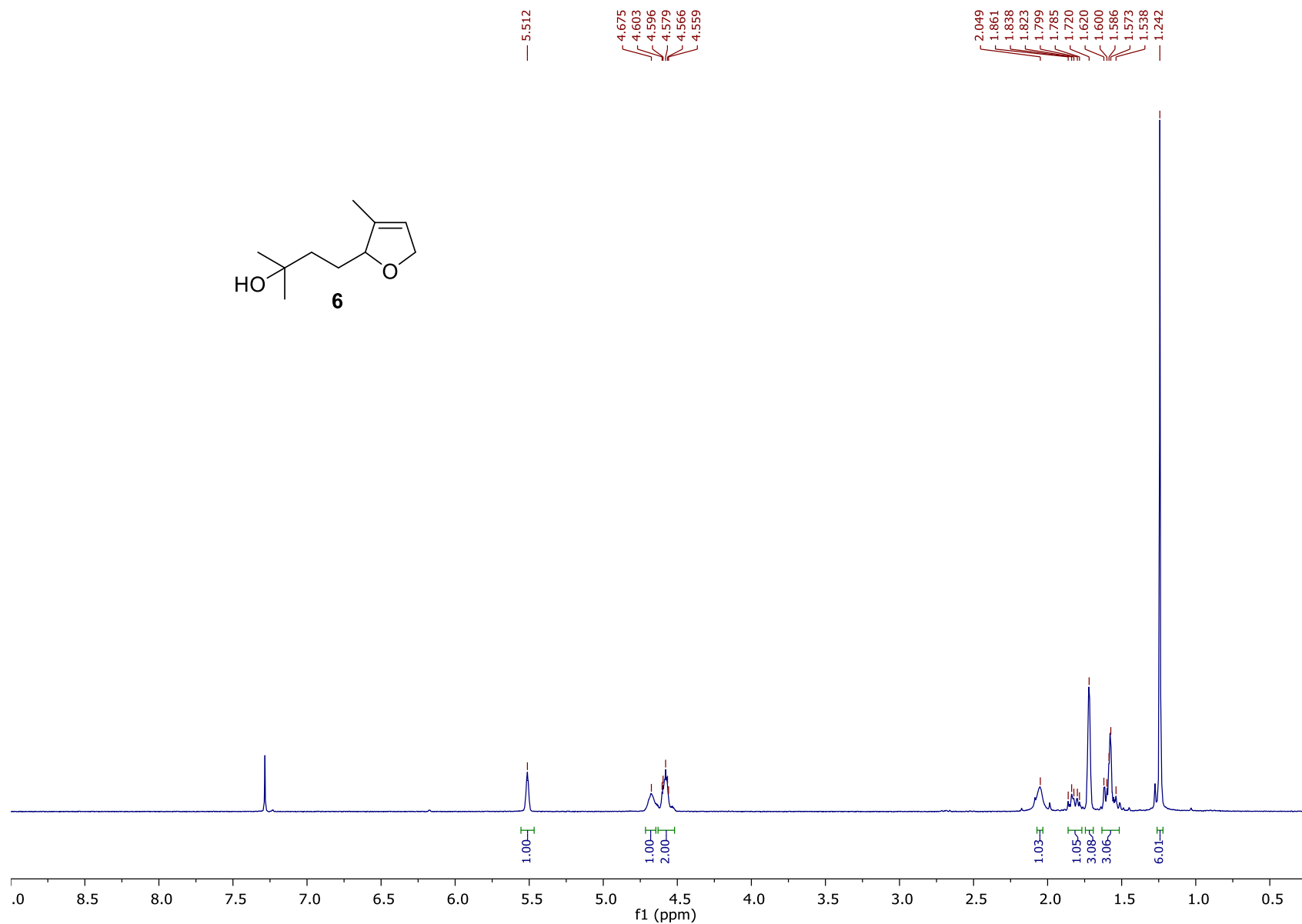
^1H NMR, DEPT 135, ^{13}C NMR and IR of 5-(buta-2,3-dien-2-yl)dihydrofuran-2(3H)-one (**5**)

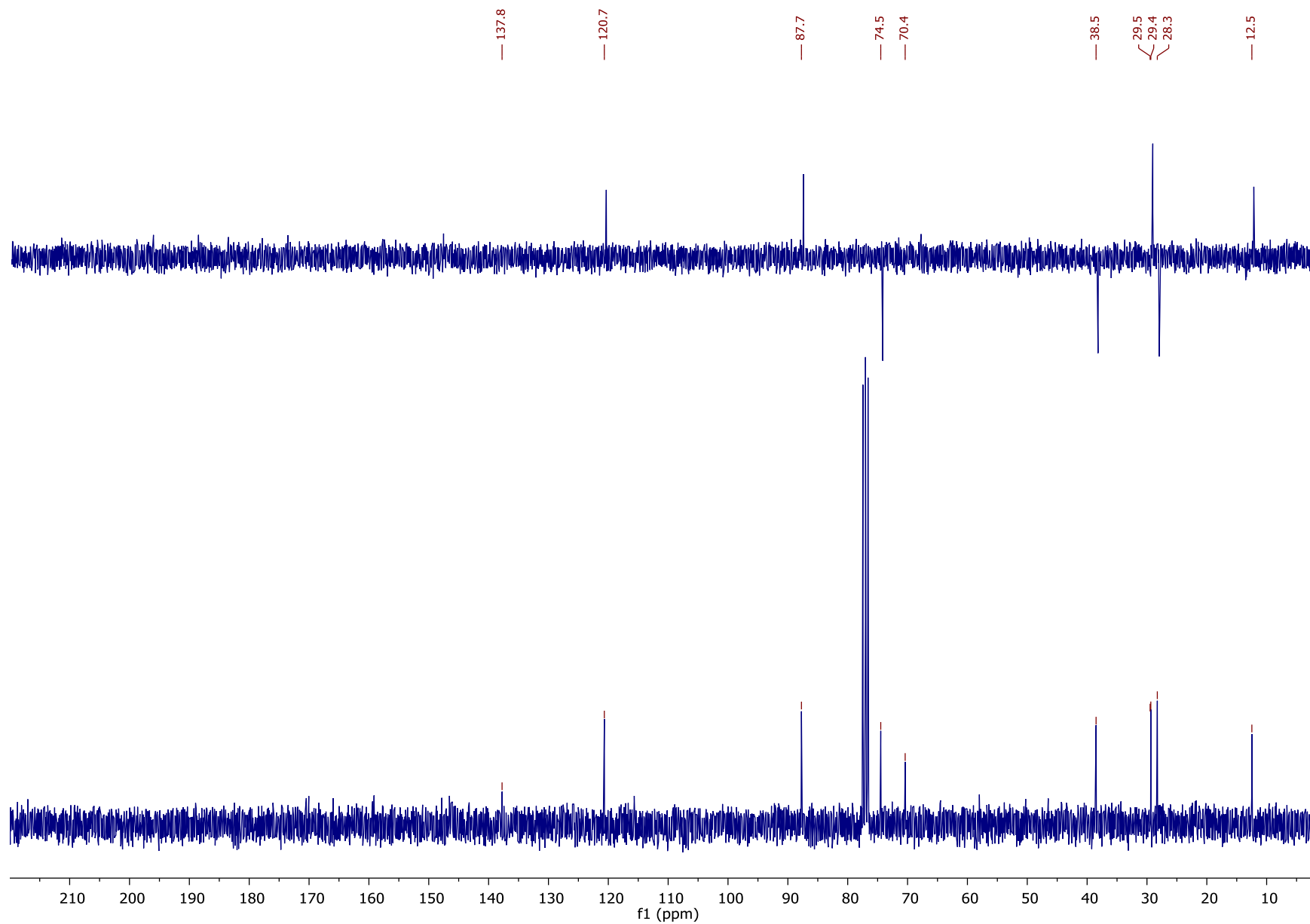


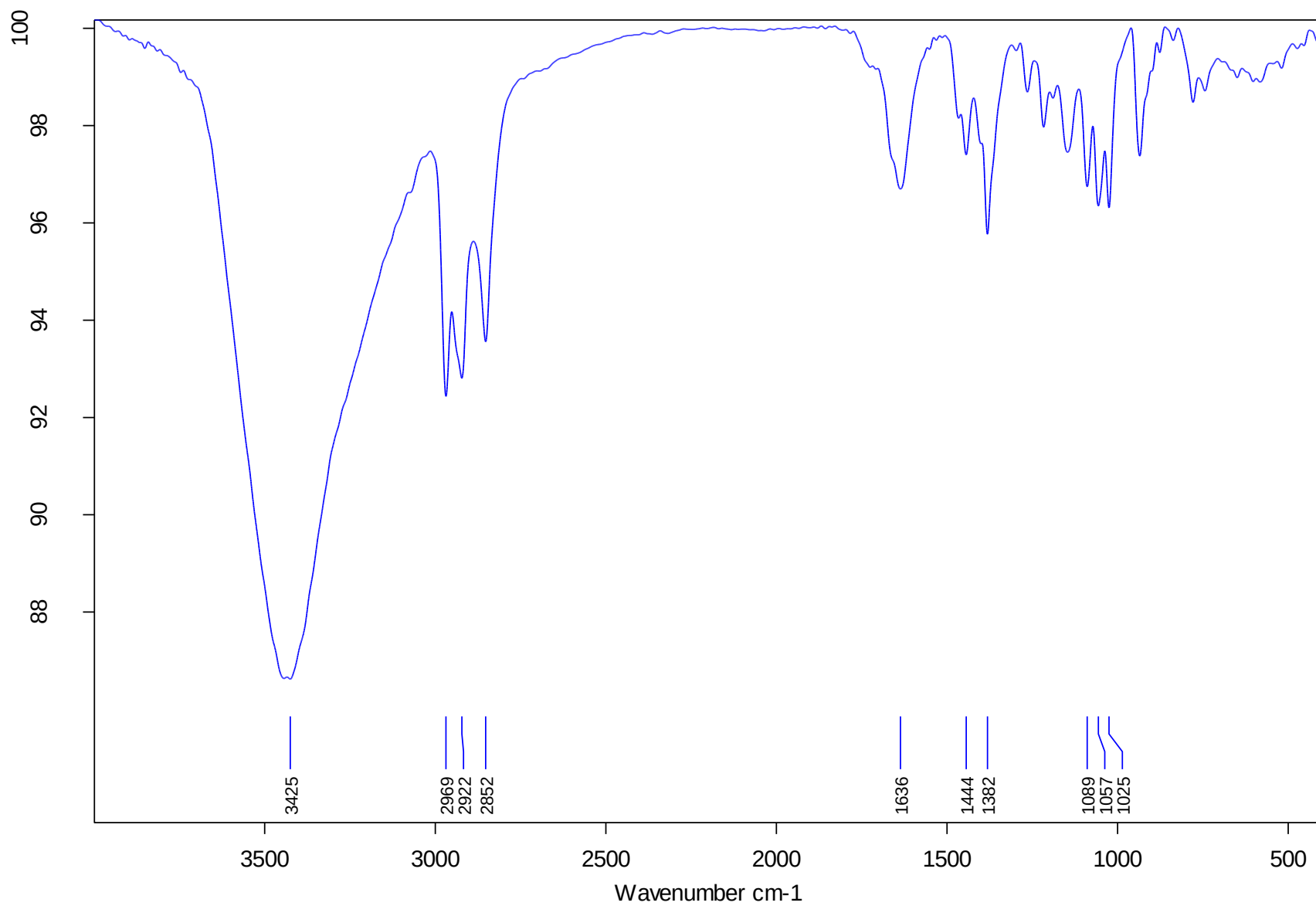




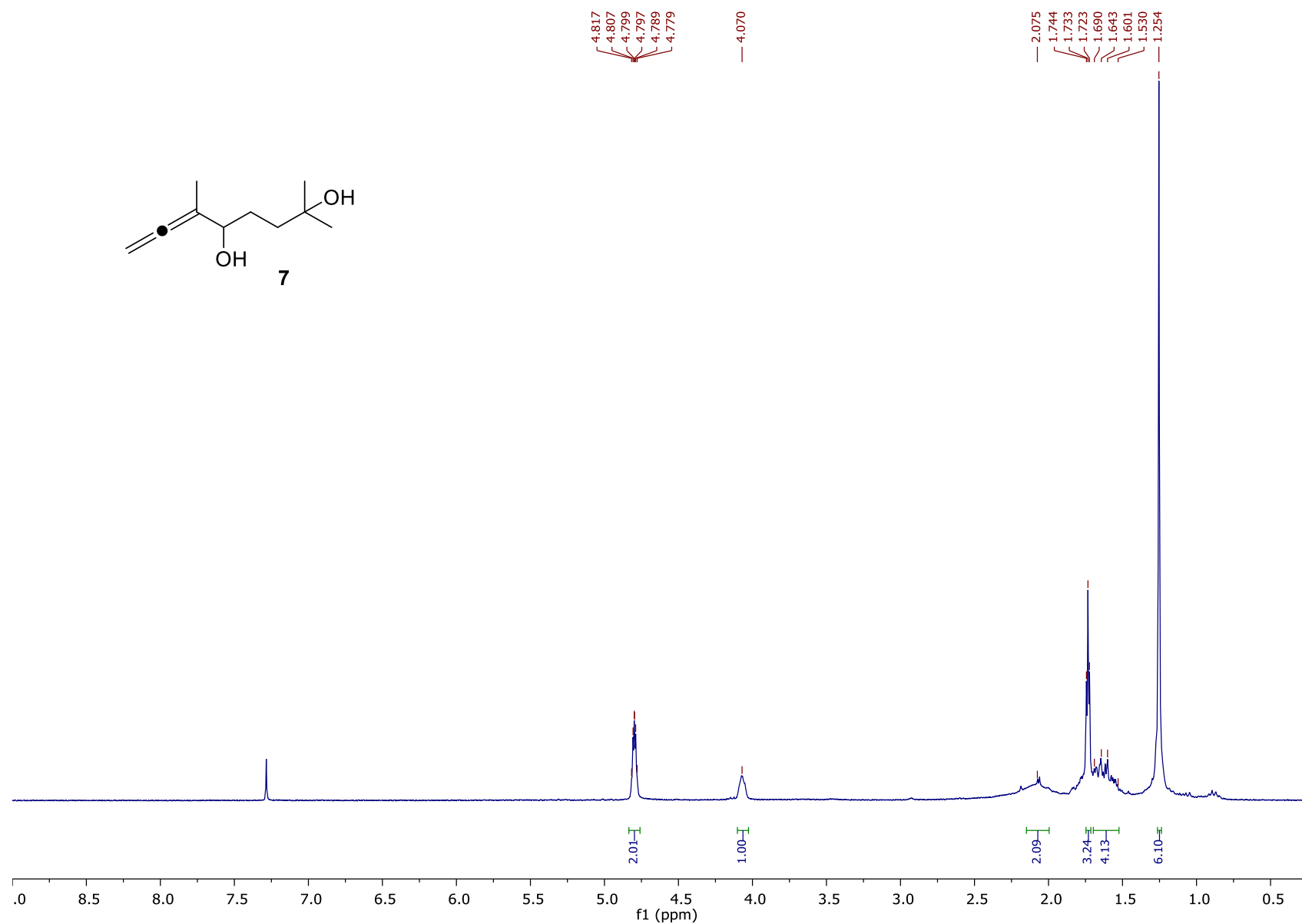
^1H NMR, DEPT 135, ^{13}C NMR and IR of 2-methyl-4-(3-methyl-2,5-dihydrofuran-2-yl)butan-2-ol (**6**)

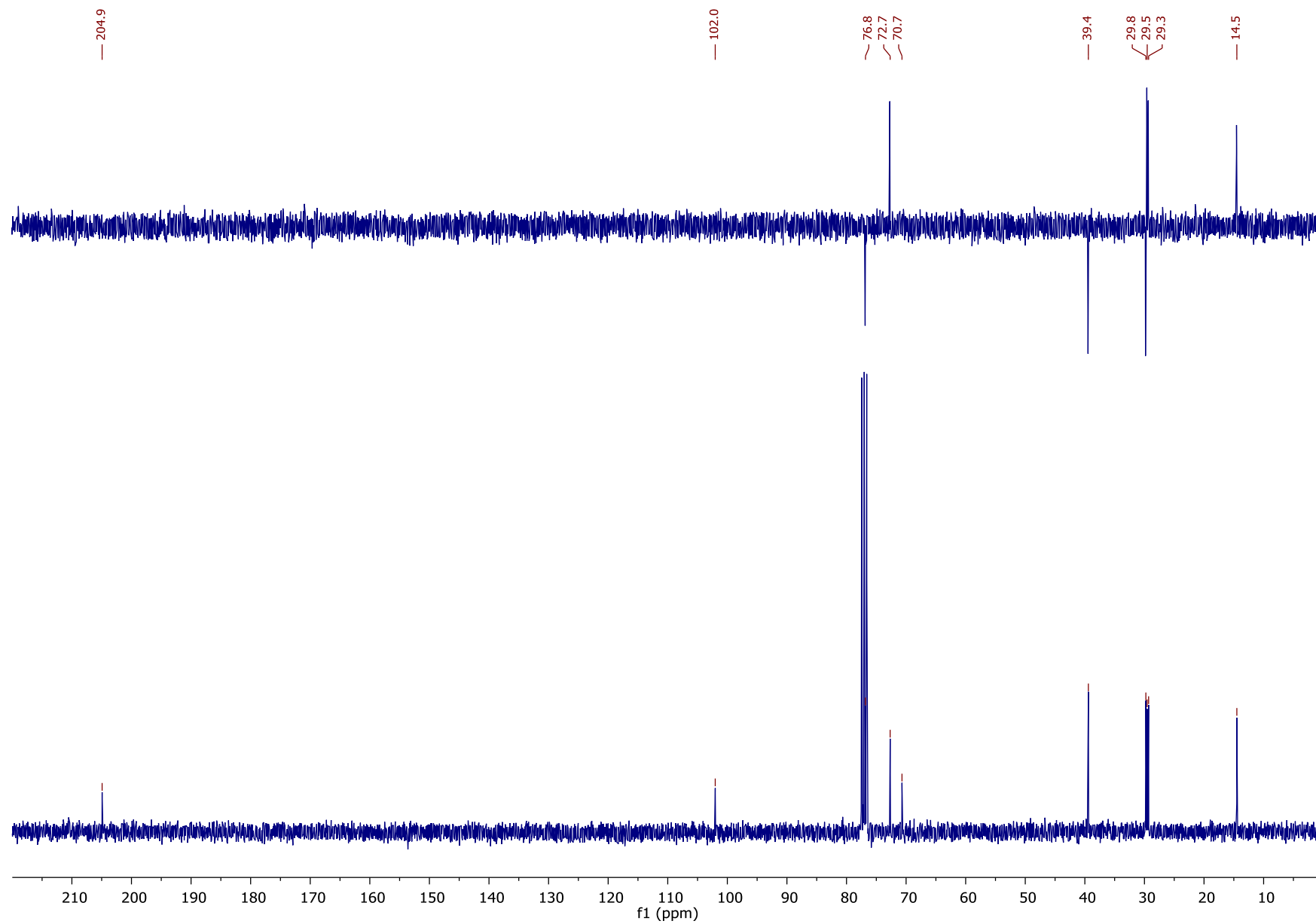


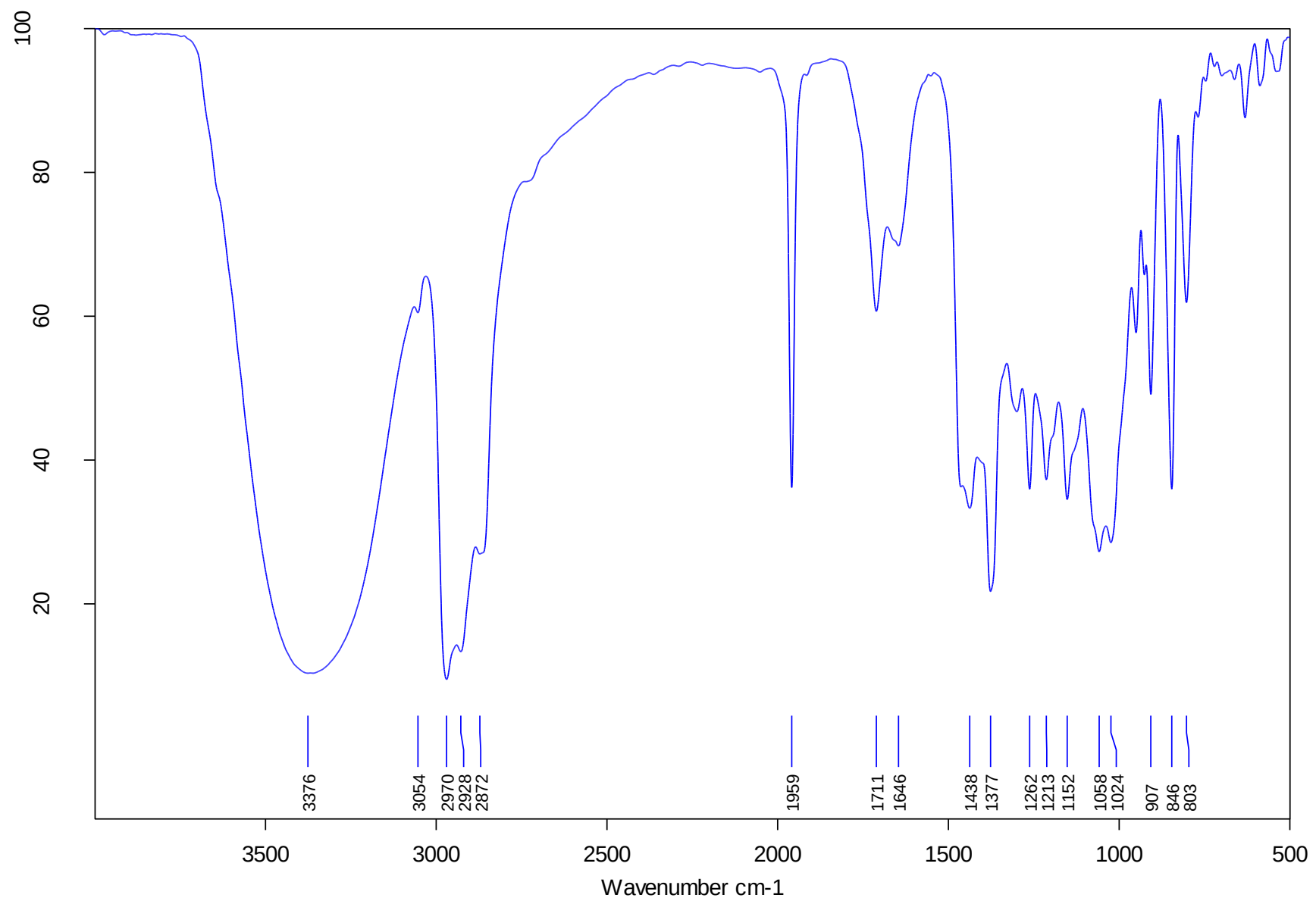




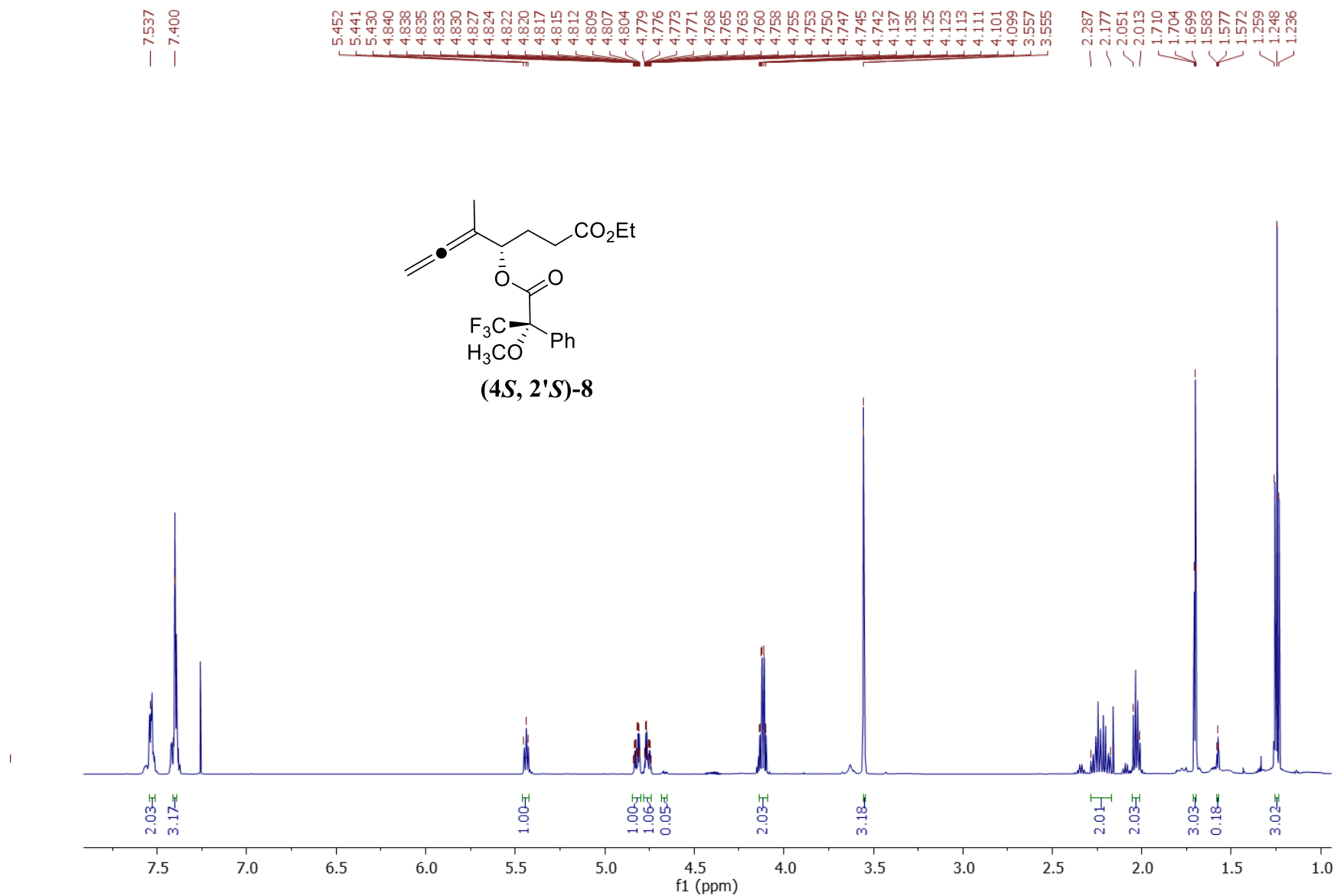
^1H NMR, DEPT 135, ^{13}C NMR and IR of 2,6-dimethylocta-6,7-diene-2,5-diol (**7**)

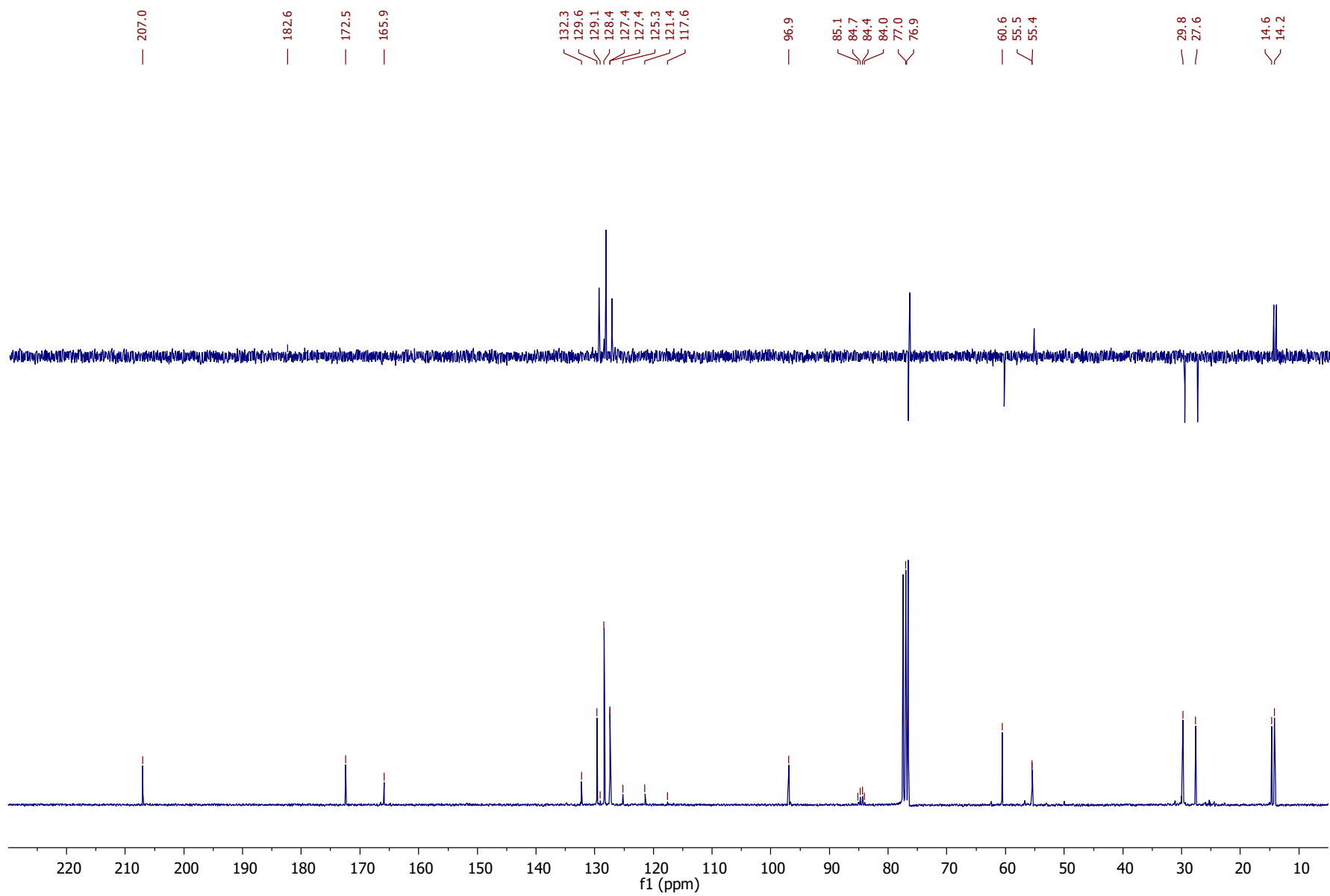




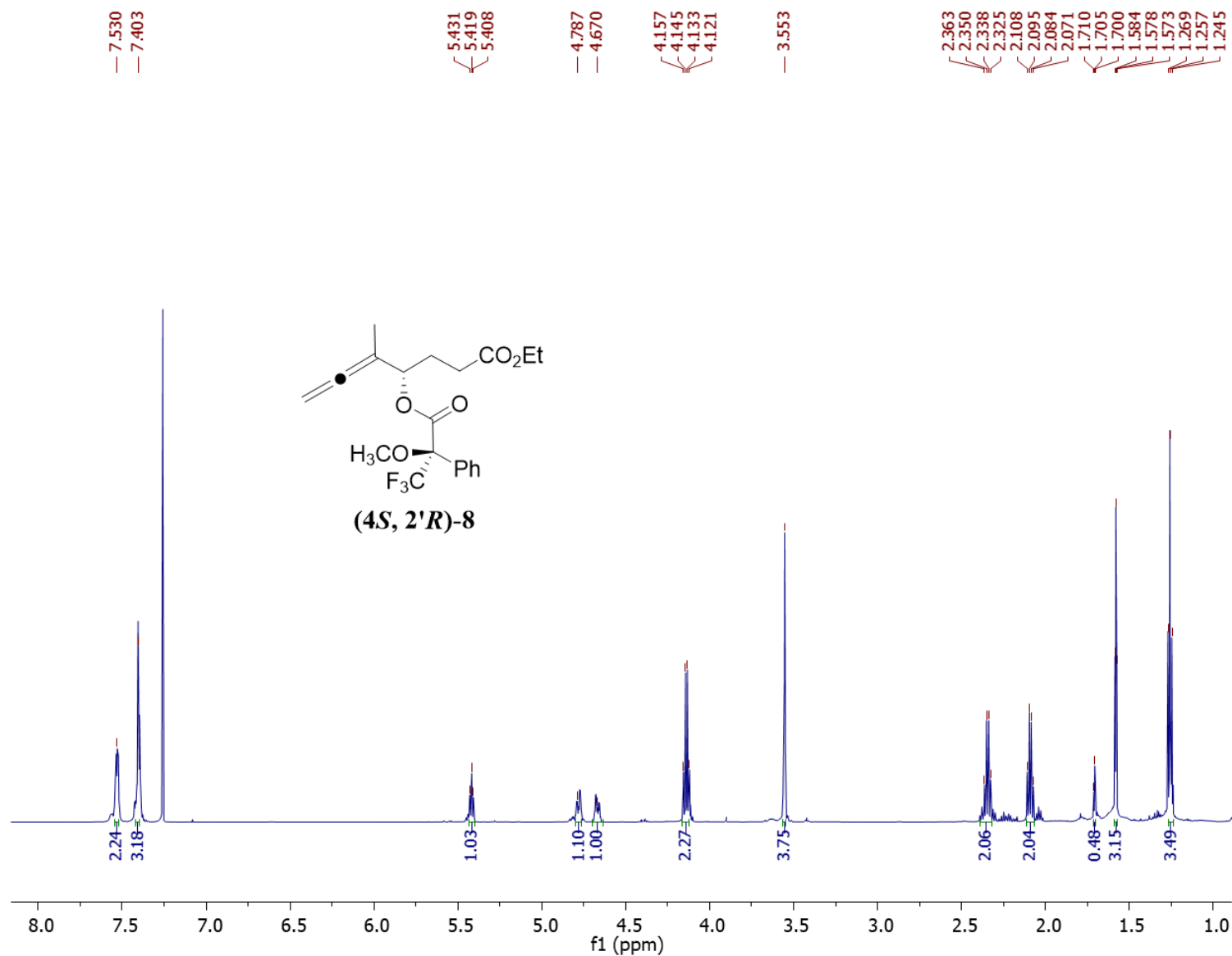


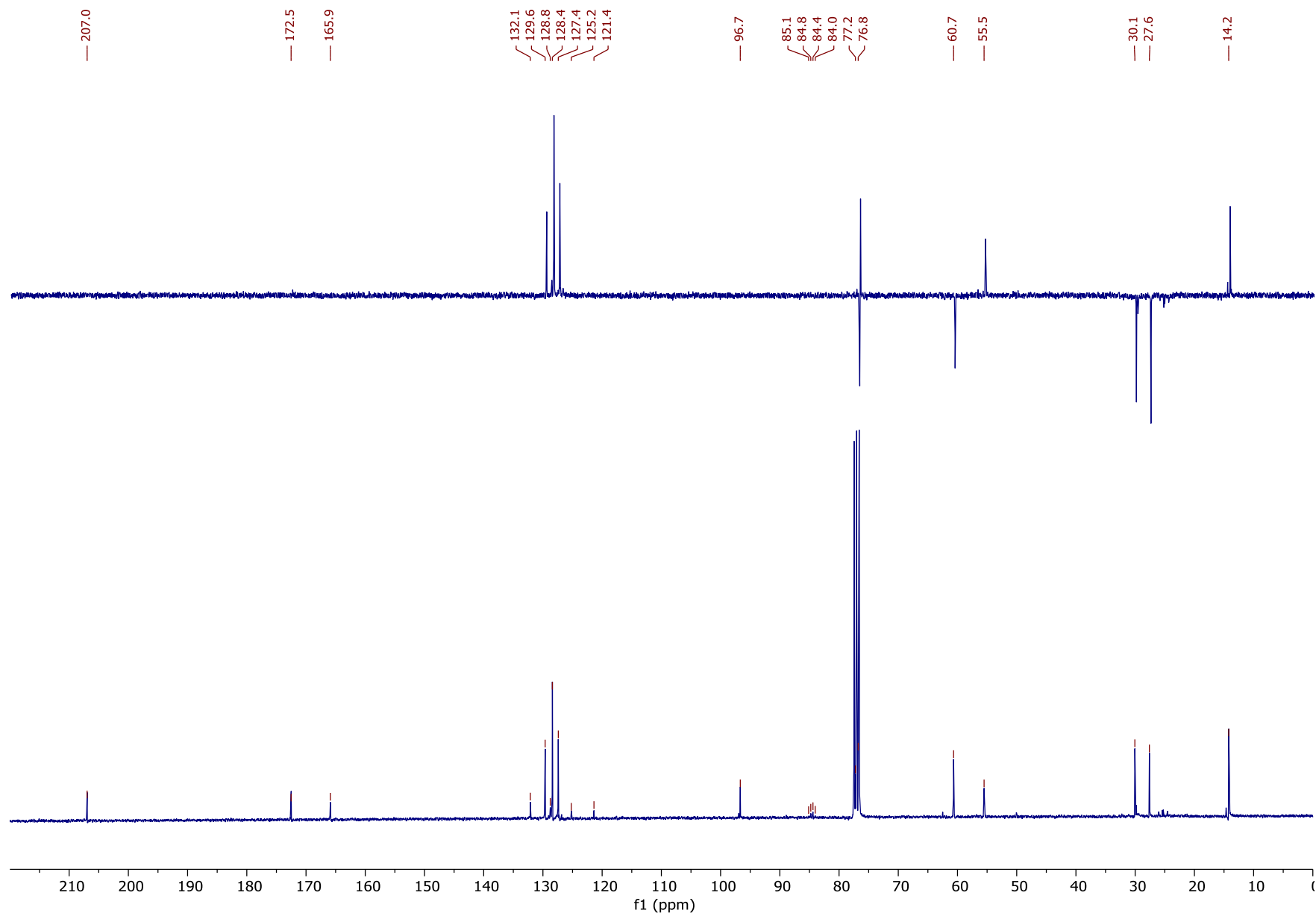
^1H NMR, DEPT 135 and ^{13}C NMR of ethyl (S)-5-methyl-4-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hepta-5,6-dienoate
 ((4*S*,2'*S*)-8)



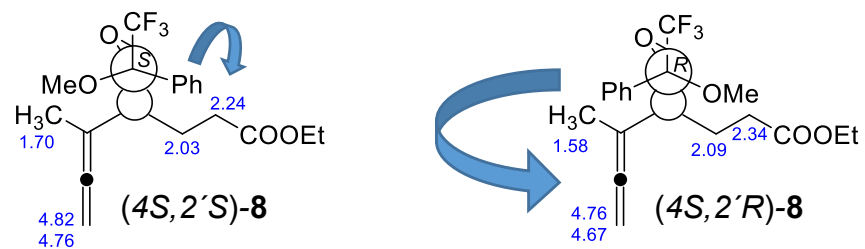


^1H NMR, DEPT 135 and ^{13}C NMR of ethyl (S)-5-methyl-4-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hepta-5,6-dienoate
 ((4*S*,2'*R*)-**8**)



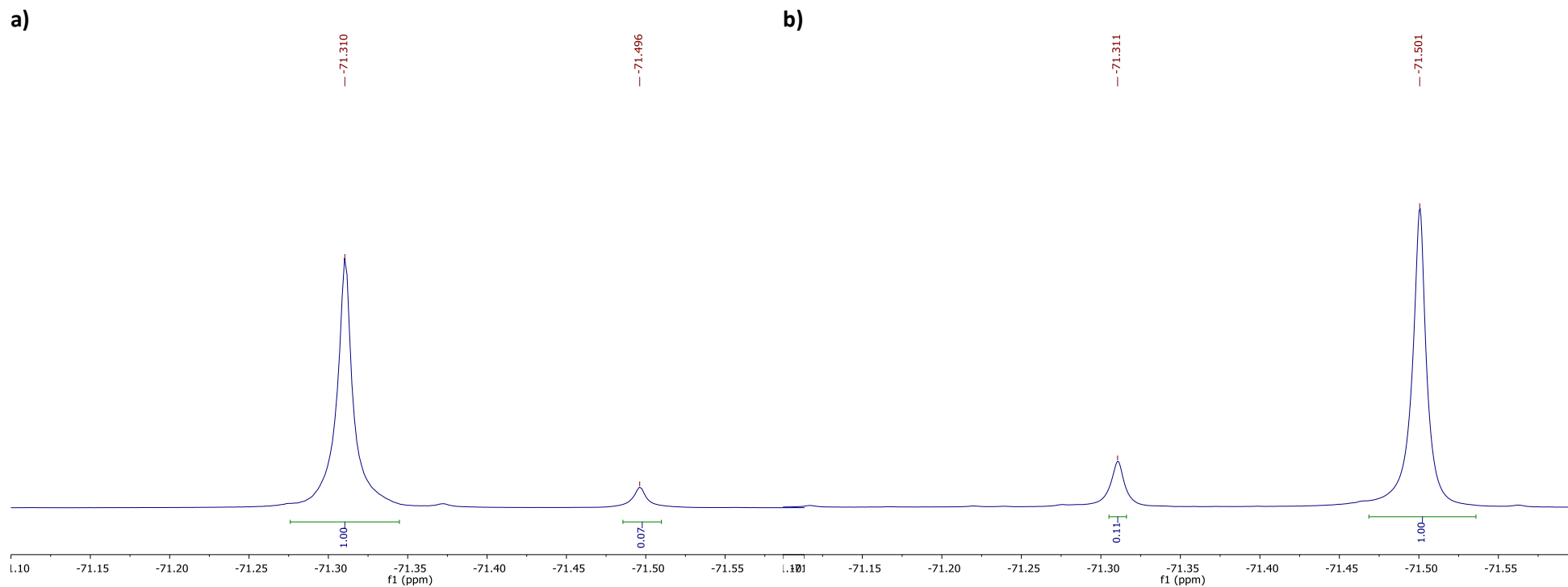


¹H NMR analysis of diastereomeric MTPA esters

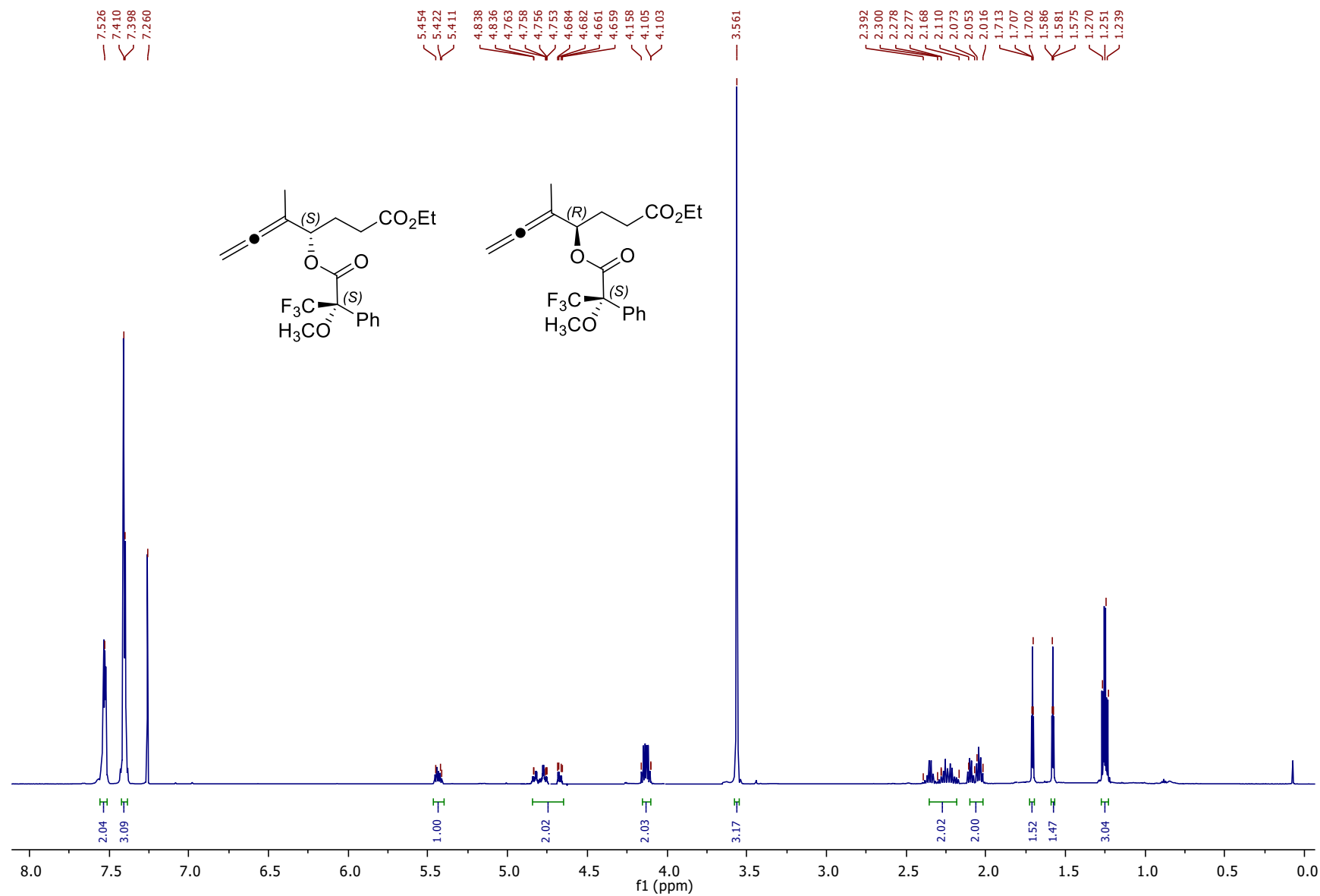


¹H NMR δ data (phenyl group shielding effect is indicated by the blue arrows in each representation)

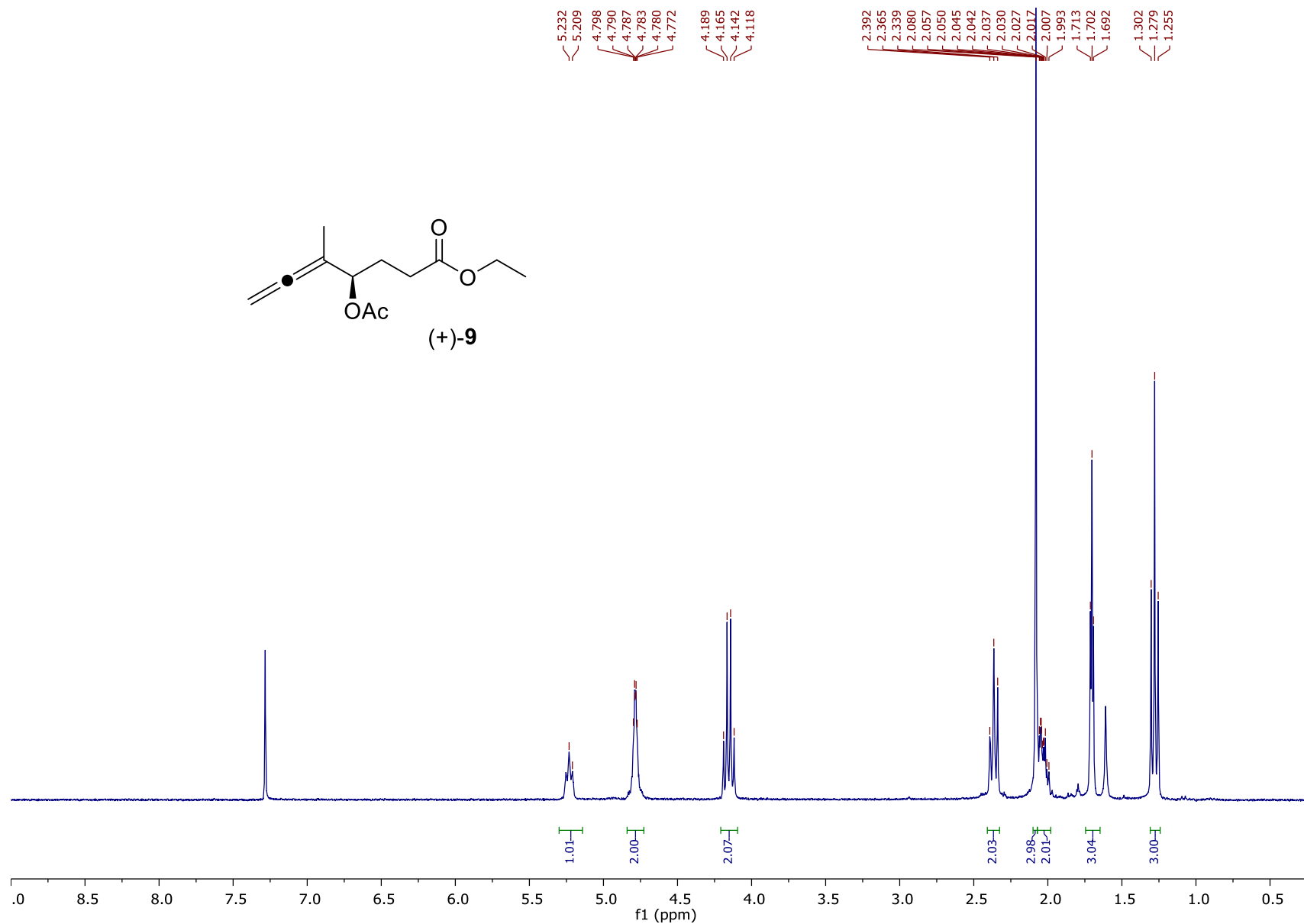
¹⁹F NMR: a) (4*S*,2'*S*)-**8**; b) (4*S*,2'*R*)-**8**

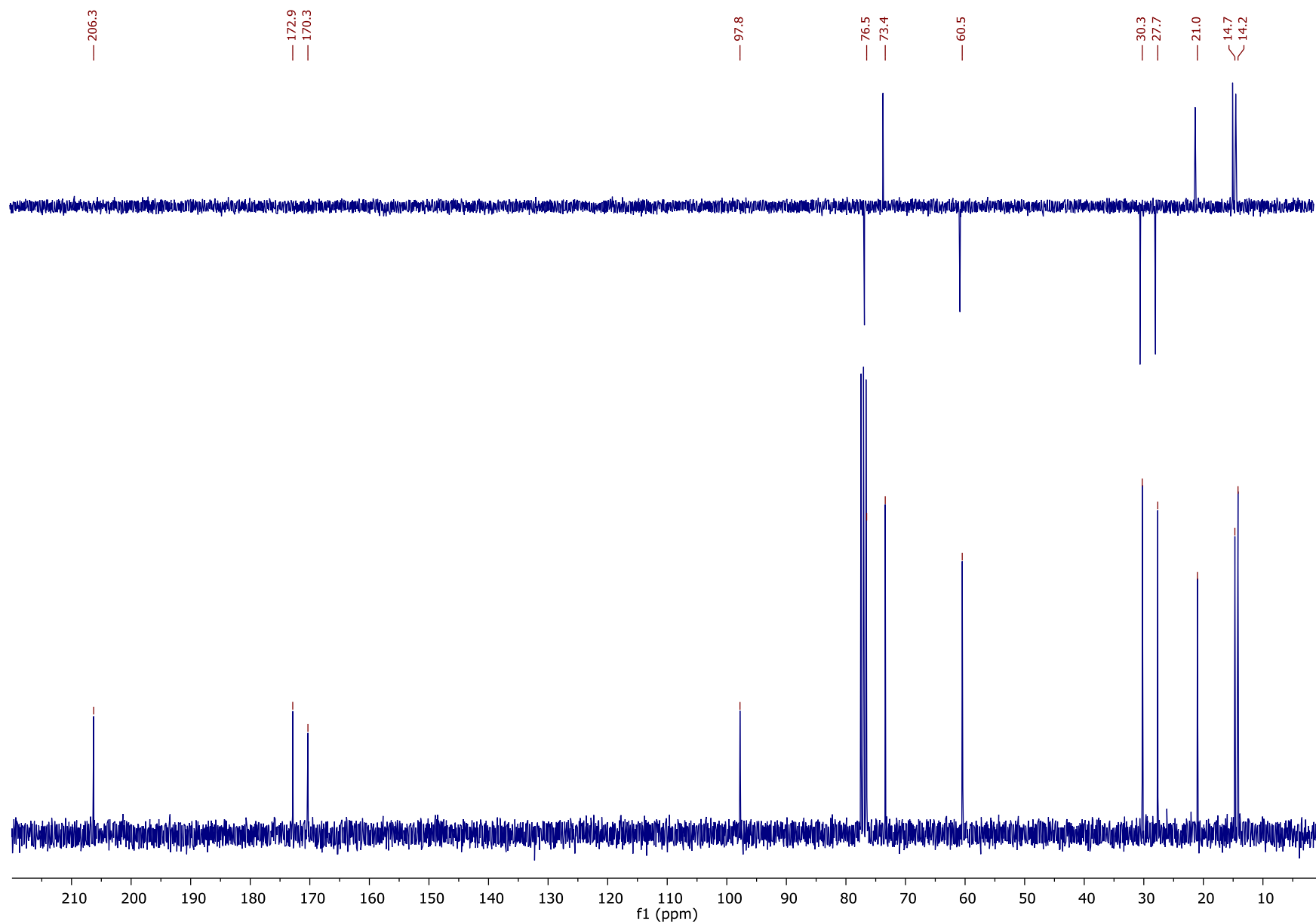


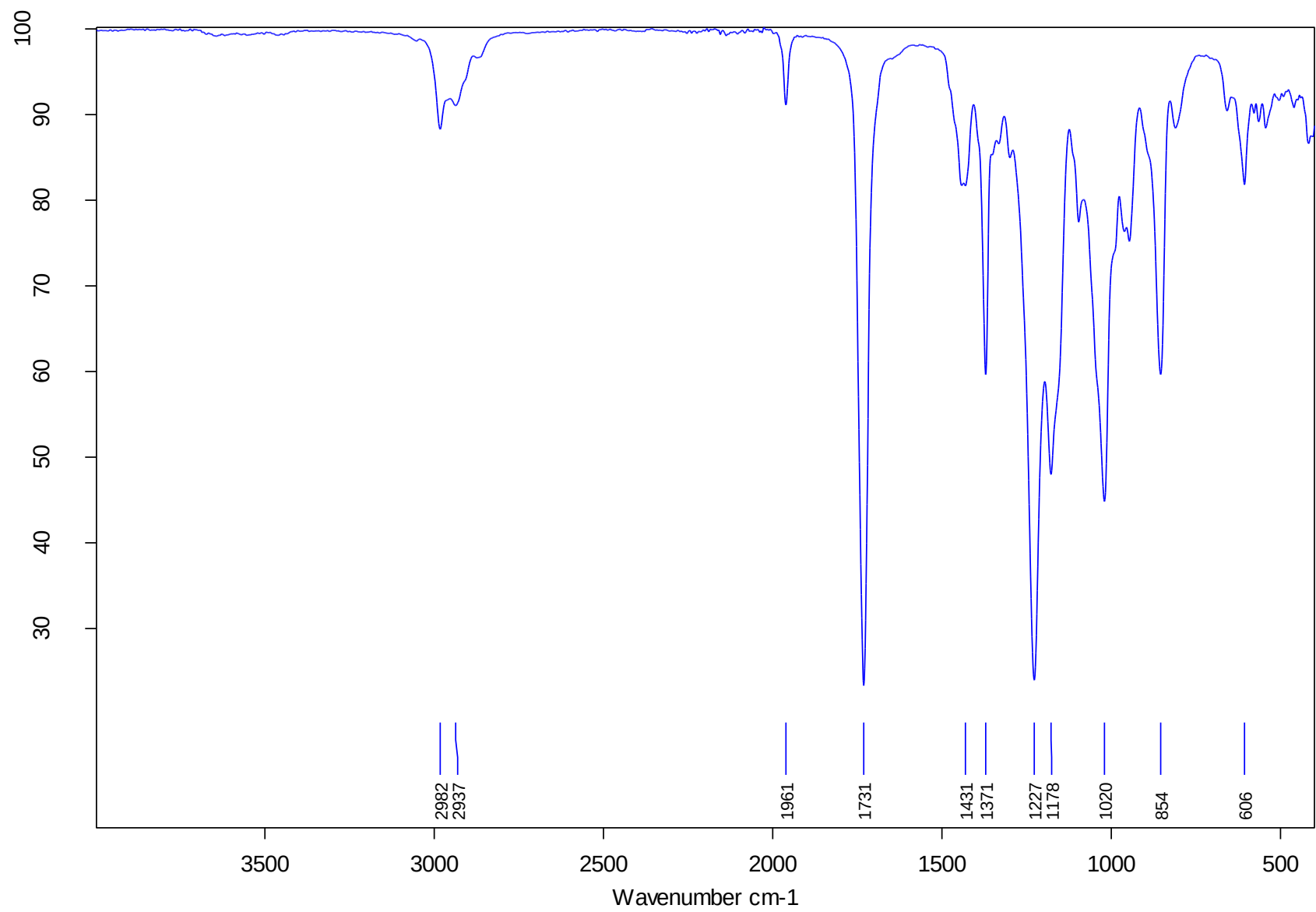
^1H NMR of diastereomeric mixture (4*S*,2'*S*)-**8** and (4*R*,2'*S*)-**8**



^1H NMR, DEPT 135, ^{13}C NMR and IR of (*R*)-ethyl 4-acetoxy-5-methylhepta-5,6-dienoate ((+)-**9**)





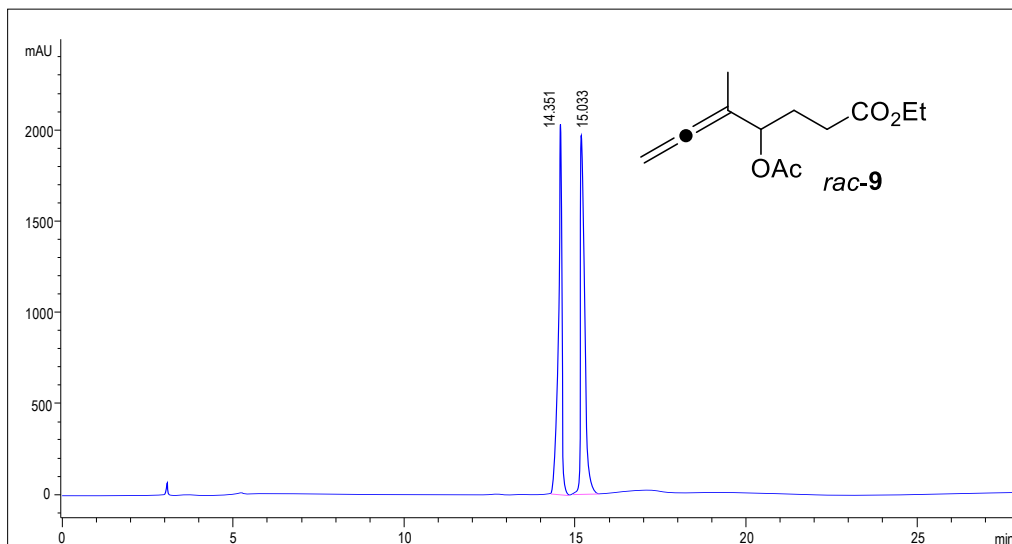


HPLC data

Ethyl 4-acetoxy-5-methylhepta-5,6-dienoate (*rac*-9)

System: Agilent 1100 series with a UV-DAD detector 210 nm. Column Daicel Chiracel OD-H

Solvent: hexane:iPrOH 99.5:0.5. Flow rate: 0.4 mL/min. Temperature: 25 °C



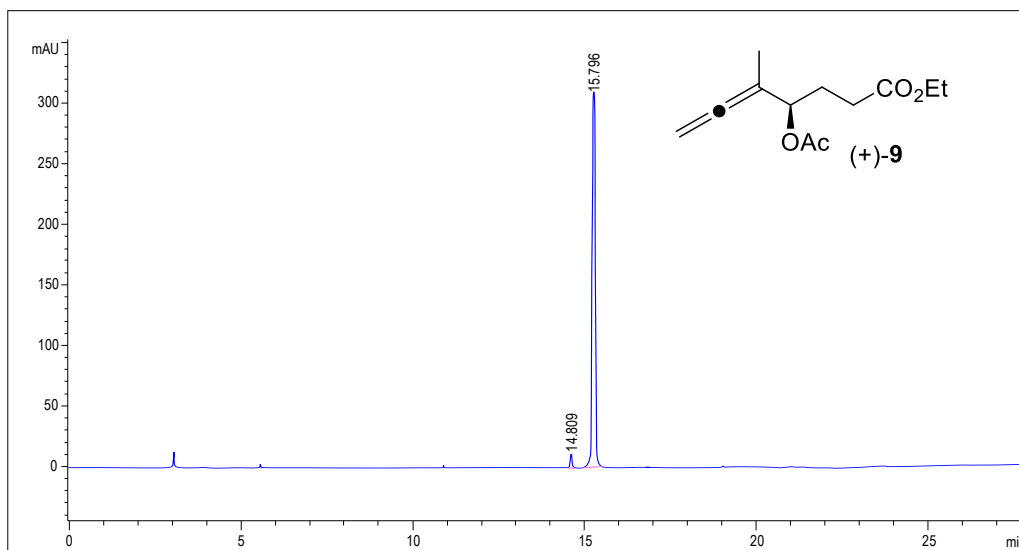
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.351	MM	0.1107	2.3657e4	2055.3609	50.0119
2	15.033	MM	0.1380	2.3645e4	1975.8990	49.9881

Totals: 47303.2237 4031.2599

Ethyl (*R*)-4-acetoxy-5-methylhepta-5,6-dienoate ((+)-9)

System: Agilent 1100 series with a UV-DAD detector 210 nm. Column Daicel Chiracel OD-H

Solvent: hexane:iPrOH 99.5:0.5. Flow rate: 0.4 mL/min. Temperature: 25 °C



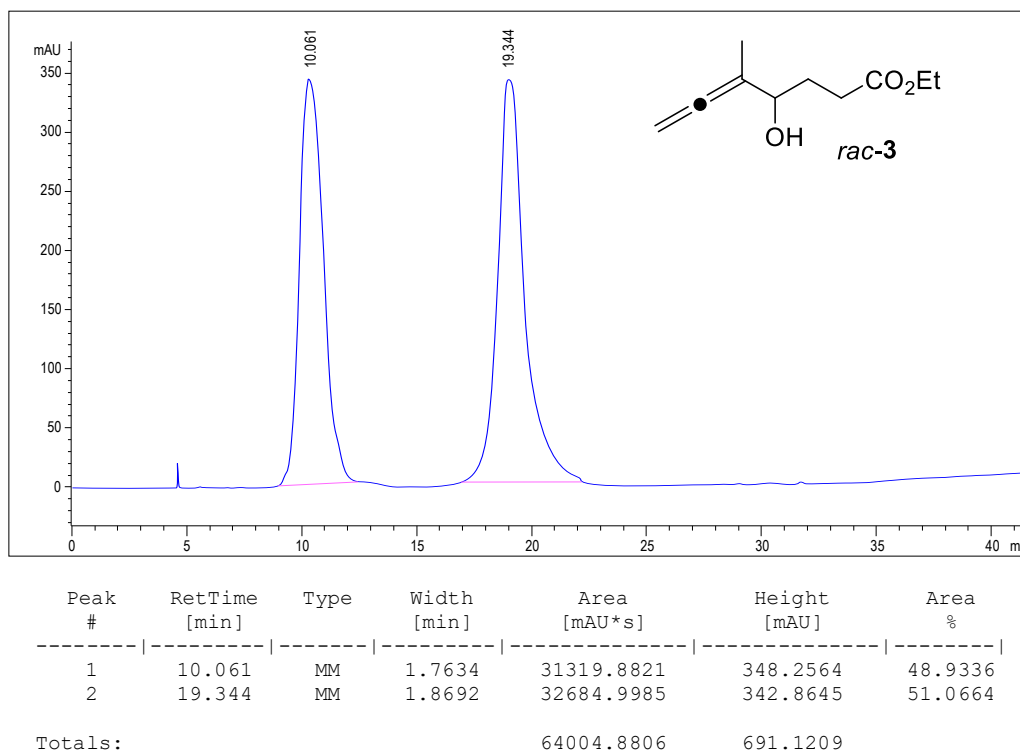
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.809	MM	0.1296	77.4528	11.9526	2.3525
2	15.796	MM	0.2075	3214.9666	309.8763	97.6475

Totals: 3292.4195 321.8289

Ethyl 4-hydroxy-5-methylhepta-5,6-dienoate (*rac*-3)

System: Agilent 1100 series with a UV-DAD detector 210 nm. Column Daicel Chiralpack IA

Solvent: hexane:iPrOH 95:5. Flow rate: 0.5 mL/min. Temperature: 25 °C



Ethyl (*S*)-4-hydroxy-5-methylhepta-5,6-dienoate ((-)-3)

System: Agilent 1100 series with a UV-DAD detector 210 nm. Column Daicel Chiralpack IA

Solvent: hexane:iPrOH 95:5. Flow rate: 0.5 mL/min. Temperature: 25 °C

